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ACTA PÆDIATRICA

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The voice of experience:

Doriden was administered to 66 children (aged between 3 and 14 years) suffering from early, middle, and late night insomnia. Treatment was initiated with a dosage of 125 mg; depending on the response, this was later raised to 250 mg — a dose which invariably proved sufficient to produce a hypnotic effect in children aged 8 years and over. Where Doriden was used as a day-time sedative, the dosage was 125 mg three times daily. By combining Doriden with hydantoin preparations it was found possible to reduce the dosage of the latter and yet avoid any increase in the incidence of cerebral attacks.

Sleep of adequate depth, lasting about 6 hours, ensued in all cases some 15–20 minutes after Doriden had been administered. Only in children with severe cerebral damage, who were given Doriden to combat motor restlessness, did the drug sometimes require more time to take effect. During sleep induced with Doriden, the pulse and respiration remained the same as during natural sleep. The children awoke rested and refreshed. In no case were any changes recorded in either the blood picture, the erythrocyte sedimentation rate, or the urine. Exanthema developed in one case only, but this subsided immediately when the drug was withdrawn.

BLECKMANN, K. H., and SALUS, D. (Kinderklin. d. Städt. Krankenanst., Essen, Germany), Beitrag zur Schlafmitteltherapie im Kindesalter. Erfahrungen mit Glutarsäureimid als Schlaf- und Beruhigungsmittel. *Med. Mschr.* (G.) *10*, 162, 1956.

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Tablets in packages of 10, 20, 100 and 500.

* T.M. Reg.

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From the Municipal Out-patient Clinic for Allergic Diseases in Children, Copenhagen, Denmark. Physician-in-chief: E. Winge Flensborg, M.D.

The Prognosis in Allergy to House Dust in Asthmatic Children Elucidated by Provocation Experiments

by ERIK RYSSING, M.D.

It is the purpose of desensitization treatment to increase the patient's tolerance to the allergens to which he is sensitive. On this account provocation experiments with these allergens before and after treatment is the best way to get information about the effect of the therapy.

Material and methods

In 1951 and 1952, 315 asthmatic children were examined in our clinic (8, 9); of which 70 children (54 boys and 16 girls) showed a positive scratch test to purified house dust plus a positive provocation test, either a sniff test and/or an inhalation test, with an immediate reaction. Sixty-three of the children (48 boys and 15 girls), aged 5 to 19 years, were followed-up in the year 1956. Seven children were unwilling to be re-examined.

During the follow-up examination the history is taken and a scratch test and one or more provocation tests with purified house dust (Boatner & Efron) are performed. The sort of provocation test, to which the patient originally reacted, is selected. 106 inhalation tests were performed on 52 children and 12 of these were given an additional sniff test. Eleven children were examined by sniff tests only. In all, 36 sniff tests were performed.

In an inhalation test the house dust extract is inhaled for 15 minutes through a mask on a Barach spray with oxygen (see illustration in reference no. 8). The test is made in a symptom-free period. Prior to this test a control inhalation for 15 minutes with a saline solution containing phenol is always made. An inhalation test is positive when auscultatory signs appear and/or prolonged cough with or without dyspnoea. When the reaction is elicited during or immediately after the test it is termed an immediate reaction; a delayed reaction is when symptoms appear 1 to 24 hours later.

A sniff test involves the insufflation of dried house dust extract into the nose. First a control test with pine pollen is made. The test is positive with the appearance of nasal symptoms. Bronchial symptoms sometimes occur.

When further provocation tests are made two or more weeks are allowed to elapse between the experiments. The majority were examined as out-patients; only a few as in-patients.

All patients but one received desensitization treatment with purified house dust extract by subcutaneous injection. We begin with a 1:1,000,000 extract of purified

house dust (Boatner & Efron) in doses of 0.1 – 0.2 – 0.4 – 0.7 ml three times a week and then the concentration is changed to the next decimal strength and so on. When the 1:1000 extract is reached we continue once a week and when the highest tolerated dose is reached the interval is lengthened to 2 weeks, 3 weeks and then a month.

The results of the inhalation experiments

Table 1 shows the results grouped according to the reaction obtained at the time of the follow-up examination. The groups are arranged in decreasing tolerance as a delayed reaction is considered to mean greater tolerance than an immediate reaction.

The first 3 groups consist of patients with a considerable increase of tolerance. The children showing either any reactions to stronger solutions than before treatment (Group 1) or delayed reactions to the same or a stronger solution than before treatment (Groups 2, 3).

The fourth group consists of 4 children who developed immediate reactions only under great disadvantages (see remarks in Table 1). The last Groups, 5 and 6, consist of 15 children with one or two immediate reactions.

To summarize then, in the first group the tolerance has increased considerably. In the second, third and fourth groups the tolerance has increased moderately. The first 2 children of the fifth group and the first 5 children of the sixth group have appreciably increased their levels of tolerance. These children showed a negative reaction to an inhalation test with a 1 per cent solution but a positive reaction when they were given an inhalation with 5 per cent of house dust solution. It is a matter of question why the increments of tolerance differ as shown. In the following, possible factors are analysed.

Factors which possibly influence the results

Table 2 shows the duration of treatment and time of observation of these 52 children. The total quantities of injected house dust allergen in milligram is shown in the third column and the intensity of treatment expressed as injected house dust allergen in microgram per month in the fourth column. It is impossible to demonstrate any evident difference between the groups.

As house dust is an allergen which affects the patients daily it was reasonable to find out if periods of vacation away from home together with continued desensitization treatment influenced the increase of tolerance. The fifth column shows no significant difference between the groups (column 11, Table 3). The last 2 columns show that the reactions to the scratch test have a general tendency to decrease after treatment.

Table 3 shows other circumstances of possible importance. There is no significant difference between the ages in which the disease has begun and

TABLE 1

The reactions to inhalation tests in 1956

Group	Number of children	Dust concentration in 1951 or 52[1] %	1 % immediate	1 % delayed	5 % immediate	5 % delayed	5 % immediate	5 % delayed	5 % immediate	5 % delayed
1. No immediate or delayed reaction	2	1/10	0	0	0	0	0	0		
	3	1	0	0	0	0	0	0		
	6	1			0	0	0	0		
	8	5			0	0	0	0		
	1	5			0	0				
2. No immediate reaction but delayed reaction to one inhalation test	1	1	0	0	0	0	0	+		
	2	1			0	0	0	+		
	2	5			0	0	0	+		
	3	5			0	+	0	0		
	2[2]	5			0	+				
3. Two delayed reactions	2	5			0	+	0	+		
4. Immediate reaction during unfavourable circumstances	1[3]	1	+	0	0	0	0	0		
	1[4]	1	0	0	0	0	+	+	0	0
	1[5]	5			0	0	+	0	0	0
	1[6]	5			0	0	+	0	0	0
5. Immediate reaction to the second inhalation test with 5 per cent house dust and/or delayed reaction to the first	1	1	0	0	0	0	+	+		
	1	1	0	0	0	+	+	+		
	1[7]	5			0	+	+			
6. Immediate reaction to inhalation test with 5 per cent	5	1	0	0	+					
	3	1			+					
	3	5			+					
	1	5			+		+			
7. Undetermined	1[8]	1	0	0	+					

[1] *Means:* The house dust concentration (in per cent) which in 1951 or 52 produced immediate reactions. [2] Unwilling to continue. [3] Attack the night before. [4] Rhonchi before inhalation. [5] Sniffing before inhalation. [6] Rhonchi before inhalation. [7] Receives continuous treatment with ephedrine. [8] Rhonchi at the time of the control inhalation test.

TABLE 2

Group	Duration of treatment in months	Time of observation after treatment in months	Total quantities of injected house dust allergen[1] in mg	Injected house dust allergen[1] mg per month	A stay away from home in months	Scratch test before treatment	Scratch test at the follow-up
1.	47	13	55	1190	0	+	+
	52	0	18	350	0	+	+
	20	30	123	6180	1	+ +	+
	39	0	53	1380	4	+ +	+
	61	0	213	3500	0	+	+
	50	0	160	3200	7	+ + +	+
	41	13	57	1400	0	+ + + +	+
	58	0	246	4250	6	+ +	÷
	48	24	176	3670	4	+ + +	+
	40	0	144	3610	3	+ +	+
	17	36	?	?	8	+ + +	+ + +
	36	0	45	1260	0	+ +	+
	40	8	119	2990	4	+ +	+
	34	0	15	470	4	+ + +	+
	19	22	41	2170	0	+ +	+
	38	0	65	1730	0	+ +	+ + +
	39	0	258	6630	8	+	(+)
	24	16	139	5800	4	+	÷
	11	13	?	?	0	+	÷
	36	15	159	4420	5	+ +	+
2.	48	0	71	1490	4	+	+
	41	11	54	1320	1	+ +	+
	36	0	40	1100	0	+ +	+ +
	2	51	0.16	80	0	(+)	÷
	0	11	0	0	0	+	+
	40	0	25	640	3	(+)	+ +
	38	0	112	2950	8	+ +	+
	20	28	?	?	0	+ + +	+ +
	17	38	?	?	4	+	÷
	20	26	70	3510	4	+ +	÷
3.	51	0	115	2260	1	+ +	+
	5	47	2.8	570	2	+ + +	÷
4.	47	0	198	4220	0	+	÷
	49	2	187	3820	0	(+)	(+)
	49	0	132	2700	4	+ + +	+
	39	0	52	1350	9	+ +	+
5.	50	0	286	5730	9	+ +	+
	36	6	113	3160	8	+ +	+
	32	10	166	5210	10	+ + + +	+ + +

[1] House dust allergen that is undiluted house dust extract prepared after Boatner & Efron.

Table 2 (*continued*)

Group	Duration of treatment in months	Time of observation after treatment in months	Total quantities of injected house dust allergen[1] in mg	Injected house dust allergen[1] mg per month	A stay away from home in months	Scratch test before treatment	Scratch test at the follow-up
6.	40	0	106	2670	8	+ + + +	+
	43	12	32	760	0	+ + +	+ + +
	57	0	14	255	0	+	+
	10	46	9	960	0	+	+ +
	38	0	59	1570	4	+ +	+
	13	27	17	1380	5	+ +	(+)
	2	64	16	8450	0	+	+ +
	69	0	209	3480	16	+ +	(+)
	31	11	41	1350	0	+	+
	39	11	112	2880	4	+ + +	+
	4	42	0.06	16	1	(+)	+ +
	51	9	175	3440	10	+	+ +
7.	48	15	16	340	5	+ + + +	+

[1] House dust allergen that is undiluted house dust extract prepared after Boatner & Efron.

the desensitization has not been started earlier in the first group than in group 5 + 6 (column 2 and 4).

As the disease has a spontaneous tendency to improve and disappear with the years, the age at the follow-up and the duration of the disease might be of importance. There is no difference between the ages in Group 1 and Groups 5 + 6 (column 3 and 5). But as the disease began earlier in the first group, the follow-up of these patients has been made on the average one year later than the follow-up of Group 5 + 6. Possibly this has a favourable influence on the results.

The columns 6–9 show that the other allergies and the treatment in consequence, change of residence, and the inheritance of allergy is apparently without importance.

The severity of the disease and the prognosis

The patients were then considered in groups according to the severity of the disease before treatment according to the principles laid down by Kraepelin (16). Table 4 shows that about half the children in Group 1 and also Groups 5 + 6 may be characterized as severe cases. Perhaps there are a few more mild cases in Group 1. In evaluating the prognosis it is to be remembered that practically all patients are treated in our clinic and therefore their symptoms are recorded exactly through the years.

TABLE 3

Group	Age on average at onset of disease in years	Age on average at start of treatment in years	Age on average at the follow-up in years	Time on average from start of disease to start of treatment in years	Time on average from start of disease to the follow-up in years	Number of patients who have received treatment with: House dust extract only	House dust extr. + vaccine	House dust extr. + other extracts	House dust extr. + other extracts + vaccine	Change of residence	Recreation	Inheritance	Total
1	$3\frac{1}{12}$	$8\frac{10}{12}$	$12\frac{7}{12}$	$5\frac{9}{12}$	$9\frac{6}{12}$	4	6	6	4	4	12	8	20
2+3+4	$2\frac{7}{12}$	$6\frac{9}{12}$	$10\frac{6}{12}$	$4\frac{7}{12}$	$7\frac{11}{12}$	3	4	3	6	4	10	10	16
5+6	$3\frac{11}{12}$	$7\frac{11}{12}$	$12\frac{3}{12}$	$4\frac{2}{12}$	$8\frac{3}{12}$	2	2	4	7	1	10	5	15
Column	1	2	3	4	5	6	7	8	9	10	11	12	

TABLE 4

Results in relation to the severity of the disease

Group	The yearly number of attacks before treatment: Less than 5	5–10	Continuous symptoms or more than 10	Undetermined	Unchanged or aggravated	Prognosis: Improved	Much improved	Symptom-free period in months: 8–11	12–17	18–23	24–29	>42	Total	Total number of children
1	6	3	10	1	1		9	3	3		4		10	20
2+3+4	6	6	4			4	8	1		1		2	4	16
5+6	2	5	7	1	6	4	5						0	15
														51

More of the children who showed a negative reaction to the inhalation test at the follow-up (Group 1) are much improved and symptom-free than of the children with immediate reactions to the inhalation test (Groups 5 + 6).

Consequently those children whose inhalation experiments are entirely negative (Group 1) have no traceable mucous membrane allergy to house dust. As so many of these children are now symptom-free or much improved this suggests that the original bronchial allergy to house dust, which has now disappeared, was important for the symptoms and the prognosis. Therefore it is of particular interest to consider those 9 children who have received treatment with house dust extract only. Table 5 shows that the prognosis of the disease is in good accordance with the results of the inhalation tests at the follow-up examination.

The results of the sniff tests

Twenty-four children originally reacted to a sniff test with house dust. Twenty-three of these children were followed-up and in 12 who originally reacted to inhalation experiments this test was now performed again. At the follow-up examination only 4 children reacted negatively to sniff tests and 2 of these had a negative inhalation test. Immediate reactions occurred in 19 children at the first and/or second sniff test whereas the following reactions to the inhalation tests were obtained. Negative reactions occurred in 4 patients, one delayed reaction in 3 patients and immediate reactions in 2. One child showed an immediate reaction during unfavourable circumstances. Three of the 19 patients had been symptom-free for more than one year.

The prognosis in a concomitant allergic rhinitis is not evaluated as the information of the records on this point are deficient and as the evaluation of the severity of the disease as a rule is very difficult.

A sniff test with the technique here employed, at which a varying and unknown portion of allergen is insufflated, is thus a very inaccurate test which does not give any information concerning the degree of sensitivity of the patients or of an existing bronchial allergy except in the few cases where bronchial symptoms are elicited.

Discussion and conclusion

While a considerable mucous membrane allergy to house dust is found before treatment demonstrated as an immediate reaction to the inhalation test, an appreciable increase in tolerance in a great number of the children is shown during the follow-up.

TABLE 5

Patients with house dust allergy only.

Group	Record no.	Severity of the disease	Duration of treatment months	Duration of observation months	Remarks	The house dust concentration which was inhaled in 1951 or 1952 with immediate reaction %	in 1956 5 % and the reactions immediate	in 1956 5 % and the reactions delayed	in 1956 5 % and the reactions immediate	in 1956 5 % and the reactions delayed
1.	92/51	Mild	41	13	Symptom-free for 27 months	1	0	0	0	0
	158/52	Mild	38	0	Much improved and symptom-free for 4 months	5	0	0	0	0
	16/52	Severe	40	0	Symptom-free for 26 months	1	0	0	0	0
	114/51	Undetermined	17	36	Symptom-free for 24 months	1	0	0	0	0
2.	123/51	Mild	2	51	Symptom-free for 52 months	5	0	0	0	+
	25/52	Mild	20	28	Much improved	5	0	+	0	0
	120/51	Severe	17	38	Much improved	5	0	+		
6.	108/51	Medium severe	2	64	Unchanged	1	+			
	29/52	Medium severe	4	0	Unchanged or aggravated	5	+			

It is impossible to evaluate completely without control material how much the increase of tolerance is due to the desensitization treatment. Such a control material does not exist in the literature either. A relationship between the results attained and the duration and intensity of treatment is not shown. This is contrary to the results of treatment of pollen allergy (1, 9) and horse allergy (18). This is possibly due to the great difference in the exposure to the allergens in question. In house dust allergy the exposure is a daily occurrence which undoubtedly maintains the sensitivity and perhaps is the cause of the variation in the increase of tolerance obtained. That is why an elimination of house dust in the home and the bedroom must be accomplished as completely as possible.

It is impossible to compare the results with the experiences of other authors, as comparable investigations on house dust allergy do not exist in literature. On the other hand Baldwin & Glaser (2) have studied a group of pollen-sensitive persons before and after treatment with pollen extract. They attempted to measure the sensitiveness of the nasal mucosa by spraying solutions with different pollen concentrations into the nose. They found an appreciable increase of tolerance in 80 out of 85 patients examined; 55 were much improved, 16 were improved and 9 unchanged. This work shows that the tolerance of allergic persons and the effect of desensitization may be evaluated using provocation experiments.

Finally, a lot of case reports and follow-up investigations of asthmatics who have received treatment with house dust extracts and possibly other extracts and vaccines, are published (4–7, 11, 13–15, 17, 18, 20–23). In these publications the diagnosis of house dust allergy has been made on a positive skin reaction only and sometimes the information is given that symptoms are produced by exposure to dust. Provocation experiments are not made. So in our opinion the diagnosis of house dust allergy is not proved as a positive skin reaction does not signify the existence of mucous membrane allergy. It is impossible therefore to evaluate the importance of house dust allergy and the results in these publications.

Conclusion: As the disease has a better prognosis in those groups with the highest tolerance during follow-up (that is, a negative or a slight reaction to inhalation of house dust) this implies that house dust allergy has been of significance in these children. Therefore patients with a proved mucous membrane allergy to house dust may claim a desensitization treatment with house dust extract. In addition dust elimination in the house ought to be carried out as extensively as possible.

Summary

Sixty-three children with primary positive provocation experiments to house dust are re-examined with provocation tests after treatment. An appreciable level of tolerance has been found in the majority.

It is impossible to demonstrate any relationship between the increase of tolerance and the duration and intensity of treatment and the age at which the treatment was started. In addition to this the duration of the disease, the age, the periods of recreation, treatment with other extracts or vaccines or the heredity do not influence the results.

The increments of tolerance correspond well to the clinical results. Due to lack of control material it is impossible to evaluate completely how much the increments of tolerance is due to the desensitization treatment. As the best results appear in the group with the highest tolerance every patient with a proved bronchial house dust allergy may claim a specific desensitization. In addition, dust elimination in the home ought to be carried out as extensively as possible.

Pronostic des troubles allergiques provoqués par les poussières domestiques chez des enfants asthmatiques, d'après les resultats d'expériences au cours desquelles ces troubles furent artificiellement suscités.

Soixante-trois enfants ayant tout d'abord réagi de façon positive aux expériences de provocation de réactions allergiques à l'égard de poussières domestiques furent soumis à de nouvelles épreuves du même genre après le traitement. La plupart d'entre eux firent alors montre d'une tolérance relativement bonne à l'égard de ces allergènes. Il s'est avéré impossible d'établir l'existence d'une relation quelconque entre le degré de tolérance et la durée ou l'intensité du traitement; il en fut de même en ce qui concerne l'âge à partir duquel le traitement fut institué. D'autre part, l'ancienneté de la maladie, l'âge du malade, la durée des périodes de récréation, les traitements à l'aide d'autres extraits ou vaccins et l'hérédité n'eurent aucune influence sur les résultats. On constata par ailleurs une bonne correspondance entre le degré de tolérance et les résultats cliniques obtenus. Vu l'absence de sujets-témoins, il n'est pas possible de déterminer exactement dans quelle mesure l'augmentation de la tolérance a été influencée par le traitement de désensibilisation. Comme d'autre part, les meilleurs résultats ont été obtenus chez les malades dont le degré de tolérance était le plus élevé, tout sujet souffrant de bronchite allergique due aux poussières domestiques, devrait faire l'objet d'un traitement de désensibilisation spécifique. Il se recommande en outre de veiller à une élimination aussi complète que possible des poussières domestiques.

Die Prognose in der Hausstauballergie bei asthmatischen Kindern auf Grund von Provokationsversuchen.

63 Kinder, bei denen primäre Provokationsversuche mit Hausstaub positiv ausgefallen waren, wurden nach der Behandlung mit Hilfe von Provokationstesten wiederuntersucht. Bei der Mehrheit wurde ein merkliches Toleranzniveau festgestellt. Es ist nicht möglich, eine Wechselbeziehung zwischen dem Toleranzniveau, der Dauer und Intensität der Behandlung und dem Alter, wenn die Behandlung begonnen wurde, nachzuweisen. Noch dazu sind die Ergebnisse von der Dauer der Krankheit, dem Alter, den Erholungsperioden, von der Behandlung mit anderen Extrakten oder Vaccinen und Erblichkeitsfaktoren nicht beeinflusst. Die Toleranzspiegel stimmt mit den klinishen

Ergebnissen gut überein. Da kein Kontrollmaterial zur Verfügung steht, ist eine vollständige Auswertung, inwiefern die Toleranzspiegel von der desensibilisierenden Therapie abhängig sei, unmöglich. Da die besten Ergebnisse in der Gruppe mit grösster Toleranz beobachtet werden, so hat jeder Kranke mit nachgewiesener bronchialen Hausstauballergie Anspruch auf eine spezifische Desensibilisierung. Noch dazu muss die Wegschaffung von Staub im Heim so gründlich als möglich durchgeführt werden.

Prognosis de alergia al polvo doméstico en niños asmáticos, elucidada por experimentos de provocación.

Sesenta y tres niños sometidos a experimentos primariopositivos de provocación con respecto al polvo doméstico, fueron examinados nuevamente con pruebas de provocación después de tratamiento. Un nivel apreciable de tolerancia fué hallado en la mayoría. Es imposible demostrar cualquier relación entre el nivel de tolerancia y duración e intensidad del tratamiento, y la edad en que fué comenzado el tratamiento. Añádese a ésto, que la duración de la enfermedad, la edad, los períodos de recreo, el tratamiento con otros extractos o vacunas o la heredad, no influencian los resultados. Los niveles de tolerancia corresponden bien a los resultados clínicos. Debido a la falta de material de comprobación, es imposible evaluar por completo en cuánto los niveles de tolerancia son debidos al tratamiento de desensibilización. Como los mejores resultados aparecen en el grupo con la tolerancia más elevada, cada paciente de comprobada alergia bronquial al polvo doméstico, puede pretender a una desensibilización específica. Debe añadirse que la eliminación del polvo casero debería efectuarse 10 más extensivamente posible.

References

1. Abramson, H. A.: Treatment of Asthma, p. 318. Baltimore 1951.
2. Baldwin, L. B. and Glaser, J.: Effect of treatment on skin and mucous membrane sensitivity and on reagins in hay fever. *J. Allergy, 8:* 129, 1936.
3. Boatner, C. H., Efron, B. G. and Dorfman, R. I.: The preparation of purified house dust extract. *J. Allergy, 12:* 176, 1941.
4. Brown, E. A., Weiss, L. R. and Bilder, M.: The house dust antigen. A critical review of the literature. *Ann. Allergy, 4:* 226, 1946.
5. Bruun, E.: Specifik desensibilisering af asthma-patienter, I–II. *Ugesk f. læger, 105:* 77 and 1245, 1943.
6. —— Specifik desensibilisering af allergiske sygdomme, III. *Nord. med., 28:* 2581, 1945.
7. —— Control examination of the specificity of specific desensitization in asthma. *Acta allergol., 2:* 122, 1949.
8. Damgård, K.: Provokationsforsøgs betydning for den specifikke behandling af asthmabørn. *Ugesk. f. læger, 113:* 1503, 1951.
9. —— Provocation experiments in asthmatic children. *Acta pædiat.*, Vol. 44, Suppl. 103, p. 107–109, 1955.
10. Feinberg, M. S.: Asthma due to house dust. *M. Clin. North Am.*, July, 44, 1927.
11. —— Allergy in Practice, p. 536. Chicago 1946.
12. Flensborg, E. Winge: The prognosis for bronchial asthma arisen in infancy after the nonspecific treatment hitherto applied. *Acta pædiat., 33:* 5, 1945.
13. —— Foreløbige resultater ved kombineret specifik og uspecifik desensibiliserende behandling af asthma bronchiale i barnealderen. *Ugesk. f. læger, 108:* 453, 1946.
14. Freeman, J.: "Rush" inoculations with special reference to hay fever treatment. *Lancet, 218:* 744, 1930.
15. Henriksen, E.: Asthma bronchiale. Thesis, Copenhagen 1951.
16. Kraepelien, S. and Engström, J.: Specifik hyposensibilisering vid asthma bronchiale hos barn. *Svenska läkartidn., 53:* 734, 1956.

17. RACKEMANN, F. M.: Studies in asthma, II. *Arch. Int. Med., 41:* 346, 1928.
18. —— Asthma. 213 "cured" patients followed up four years later. *Arch. Int. Med., 50:* 819, 1932.
19. RYSSING, E.: Allergy to horses among asthmatic children in Copenhagen. *Ugesk. f. læger, 118:* 299, 1956.
20. SALÉN, E. B.: Karl Hansen, Allergie, p. 313, Leipzig 1943.
21. SECHER, K.: Bemærkninger om asthmabehandling. *Nord. med., 16:* 3649, 1942.
22. SUTHERLAND, C.: The preparation of house-dust extracts. *Brit. M. J., 2:* 280, 1942.
23. UNGER, L., UNGER, A. H. and WOLF, A. A.: Bronchial asthma in children: treatment and results. *Ann. Allergy, 10:* 574, 1952.

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EEG Findings in Concomitant Strabismus and Other Ocular Diseases

by A. FOIS and R. FREZZOTTI

Abnormal EEG findings can be present in patients with different ocular diseases, e.g. strabismus, glaucoma, congenital cataract, infantile glaucoma, retrolental fibroplasia, palpebral ptosis. This has been shown by Dyer & Bierman (1), Stillerman, Gibbs & Perlstein (8), Parson-Smith (6), Steiger & Wurth (4), Gibbs, Fois & Gibbs (3), Levina & Neuschtadt (5), Hartmann (4); in a former paper (2) we described electroencephalographic findings in a group of 83 patients, most of whom had either glaucoma or strabismus.

This investigation has been restricted to a special group of patients, i.e. children whith strabismus and other ocular diseases.

Technique

A Galileo mod. 32 eight channels apparatus has been employed throughout this study. Silver disc electrodes have been fastened with cotton and collodion to different scalp areas, a minimum of 10 exploring electrodes being used. The electrodes were applied to frontal, central, temporal, anterior temporal and occipital areas, using more leads when deemed necessary. The reference electrodes were situated in the ear lobes, both ears or the left or right being used according to the requirement of each individual case. The record has been carried on in every patient during the waking state, spontaneous sleep and on wakening. When necessary a small amount of Nembutal (10 to 80 mg) was administrered in order to induce sleep. As abnormal have been considered records with evident seizure activity or diffuse or focal slowing; as slightly abnormal the records with amplitude asymmetries between symmetrical leads and fast activity between 25 and 35 cycles/sec.

Material

The present series includes syndromes of different nosographic personality: some obviously malformative, others still of undetermined origin.

Concomitant strabismus, in most cases without signs of CNS involvement, was present in 80, congenital cataract in 10, infantile glaucoma in 5, congenital ptosis in 3, familial congenital macular degeneration in 3, Laurence-Moon-Biedl-Bardet

TABLE 1

EEG findings in miscellaneous ocular diseases.

EEG findings		Age up to 10 yr			Type of strabismus		Amblyopia		
					alternating	constant	absent	present	not classified
No. of cases:		37	22	21	27	53	26	51	—
Normal	40	13	13	14	15	25	14	26	—
Abnormal	40	24	9	7	12	28	12	25	3
14+6 pos. spikes	17	8	7	2	5	12	4	12	1
Diffuse spike and waves	4	2	1	1	2	2	2	2	—
14 and 6+spike and waves	7	6	—	1	2	5	2	5	—
Occipital foci	6	6	—	—	2	4	1	3	2
Multiple foci	1	1	—	—	—	1	—	1	—
Asymmetry	1	—	1	—	1	—	1	—	—
Fast	1	—	—	1	—	1	—	1	—
Small sharp spike	3	1	—	2	—	3	2	1	—
Percentage af abnormal findings	50 %	64.86 %	40.90 %	33.33 %	44.44 %	52.83 %	46.15 %	49.01 %	—

TABLE 2

EEG findings in different types of strabismus.

	Congenital cataract	Familial mac. degeneration	L.M.B.B. syndrome	Keratoconus	Infant. glaucoma	Congenital ptosis	Cong. oc. palsy
Total cases	8	3	3	1	4	3	2
Normal	4	—	—	—	4	2	2
Abnormal	4	3	3	1	—	1	—
14 and 6 positive spikes	1	2	2	—	—	1	—
Diffuse spike and waves	1	—	—	1	—	—	—
Multiple foci	2	—	1	—	—	—	—
Frontal foci	—	1	—	—	—	—	—

(L.M.B.B.) syndrome in 3, keratoconus in one and congenital palsy of ocular muscles in 2 of the patients studied. The results of EEG investgation have been summarized in Tables 1 and 2.

Results

From the data given in Tables 1 and 2 it is evident that the percentage of abnormal findings must be considered in comparison with that of a "normal" childhood population (about 10%). The abnormal findings in

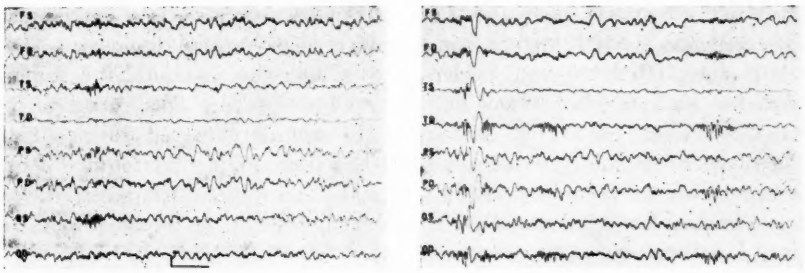

Fig. 1 (*left*). Strabismus. Light sleep: 14/sec positive spike discharges on the left temporo-parieto-occipital leads. Fig. 2 (*right*). Strabismus. Light sleep: very frequent high voltage 14/sec positive spike discharges on the right temporo-parieto-occipital leads, spreading with negative signs to the frontal region, sometimes followed by rudimentary negative spike and slow waves.

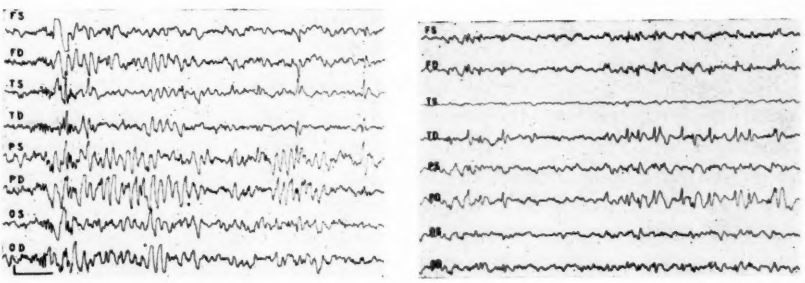

Fig. 3 (*left*). Strabismus. Light sleep: 14/sec positive spike discharges, more evident on the left hemisphere, sometimes followed by slow waves and spike focus left parieto-temporal region. Fig. 4 (*right*). Pigmentary degeneration of the retina. Light sleep: spike focus right parieto-temporal region.

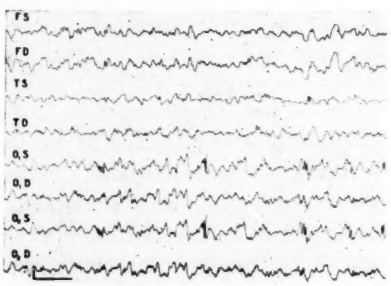

Fig. 5. Congenital glaucoma. Light sleep. Multiple spike discharges left occipital leads.

our study are mainly spike and wave diffuse discharges, cortical spike foci, mostly in the occipital region, and 14 and 6 positive spike discharges. The latter abnormality has been evidenced by Gibbs who considered it possibly of diencephalic origin, but this has not yet been proved. This abnormality has been observed almost exclusively in records obtained during light sleep; moreover this type of discharge has been frequently found by us in immediate temporal association with spike and waves diffuse discharges. Such finding has been observed not only in the present study, but also in children with behaviour disorders with normal I.Q. or mental deficiency, in cyclic vomiting, paroxismal abdominal pain, stuttering, juvenile thyroiditis and other syndromes in which a diencephalic component can be supposed. To these remarks must be added the beneficial influence of barbiturates and hydantoin observed in such patients.

Two patients with L.M.B.B. syndrome also showed 14 and 6 positive spike discharges.

Discussion

Significant can be considered the high percentage of EEG abnormalities found in concomitant strabismus. Seizure discharges, mostly diffuse, sometimes focal, have been found; abnormal records seem to be equally frequent among cases with alternating strabismus and unilateral strabismus, as well as among cases with or without amblyopia. In the series of Stillerman the more frequent EEG finding was the presence of occipital spike foci. This is also what one of us has observed in children with retrolental fibroplasia (3). In the present series diffuse discharges have been more frequently found. This discrepancy can be explained with the different type of patients considered, almost entirely represented in our series by children with a normal I.Q. and without neurological signs.

It is consequential to relate our findings with the problem of the etiology and pathogenesis, particularly as the strabismus is concerned. An interference of the CNS can be inferred, an alteration in function being possibly localized either in the diencephalo-mesencephalic system or in the cortical grey matter. The hypothesis of Keiner who considers a retardation of myelinization to be important in the pathogenesis of strabismus is worth mentioning here. The EEG findings are further evidence, besides clinical observation, that barbiturates and similar drugs are of value in such cases. In the other ocular diseases listed in Table 2, EEG abnormalities appear to be more frequent in the group in which the pathology concerns mainly tissues of ectodermal origin, like the L.M.B.B. syndrome, macular heredodegeneration and congenital cataract.

We would like to reemphasize here the therapeutic implications. Frequent

improvement in the ocular symptomatology in strabismus can be obtained with drugs such as the barbiturates, hydantoin and more recently with rauwolfia, chlorpromazine and meprobamate. These drugs improve also the abnormalities in behaviour very often associated with concomitant strabismus. We would also like to point out that phenobarbital has been employed by us in the treatment of strabismus particularly in the concomitant variety. This therapy has been in fact very efficient in such syndrome, together with surgical treatment, which although necessary, does not touch the real problem of the etiology of the strabismus.

Conclusions

Summarizing our data it can be concluded that in the group of patients examined a high percentage of EEG abnormalities, mostly seizure discharges, has been detected. For this reason an interference of the CNS in these states must be seriously considered. It cannot be stated from the present study if these findings might be considered the only explanation regarding the pathogenesis in the group of syndromes examined. Moreover, further investigation is needed to find out if these abnormalities are the result of specific noxious agent affecting different levels of the CNS or tissues of similar embryogenic origin.

Our thoughts must be directed toward the possibility that the CNS is involved in the pathogenesis of these syndromes. This appears to be of considerable importance in so far as therapy is concerned.

Addendum

Since the present paper was submitted for publication, 10 additional cases of strabismus have been observed; 7 had EEG abnormalities. Moreover 6 cases of pigmentary degeneration of the retina have been examined: in 2 initial cases the EEG was normal, in the others 14 and 6 positive spikes discharges have been observed. Three additional cases of congenital cataract had records within normal limits.

Summary

An EEG investigation in various ocular diseases has been carried out. Strabismus was present in 80 cases, congenital cataract in 10, infantile glaucoma in 5, congenital ptosis in 3, Lawrence Moon Biedl syndrome in 3, keratoconus in 1, congenital ocular palsy in 2. The patients examined were almost exclusively children. Clear cut EEG abnormalities have been found in 50 % of cases with strabismus.

Regarding the other syndromes, the number of subjects examined is not sufficient to make a percentage. However, the majority of normal records have been found among

cases with infantile glaucoma, congenital ptosis and congenital ocular muscular palsy. The EEG abnormalities were mostly diffuse spike and waves and 14 and 6 positive spike discharges and less often epileptogenic cortical foci. Minor abnormalities (asymmetries, fast frequencies, small sharp spikes) have been recorded in a small percentage of cases.

Données électro-encéphalographiques en cas de strabisme concomitant et d'autres maladies oculaires.

On a executé l'électro-encéphalogramme sur 80 cas de strabisme concomitant, 10 cas de cataracte congénital, 3 cas de hérédodégénération de la macula, 3 cas de syndrome de Lawrence, 1 cas de kératocône, 2 cas de paralysies congénitales des muscles oculaires. Il s'agissait surtout d'enfants. On a observé des alterations électro-encéphalographiques marquées dans 50 % des cas de strabisme. En ce qui concerne les autres affections, le nombre n'est pas suffisant pour que l'on puisse énoncer des pourcentages. Il est à souligner le fait que l'on a trouvé des tracés normaux dans les glaucomes infantiles, dans les ptosis congénitaux des muscles oculaires avec une nette prépondérance pathologique dans les autres. Les altérations électro-encéphalographiques étaient représentées par des foyers corticaux d'activité épileptique, des décharges de pointes ondes diffuses et de pointes positives de 14–6 c/s. Des altérations moins considérables (asymetries, rythmes rapides, petites pointes) ont été remarquées dans un petit pourcentage de cas de strabisme.

EEG-Funde bei konkomitierendem Strabismus und anderen Augen-Krankheiten.

Bei 80 Fällen von konkomitierendem Strabismus, bei 10 Fällen von angeborenem Star, bei 5 Fällen von kindlichem Glaucom, bei 3 von angeborener Ptosis, bei 3 von Heredodegeneration der Macula, bei 3 Fällen von Lawrence'schem Syndrom, bei einem Fall von Keratokonus und bei 2 Fällen von angeborener Paralyse der Augenmuskeln, im überwiegenden Teil bei Kindern, wurde das Elektroencephalogramm ausgeführt. Deutliche elektroencephalographische Veränderungen sind bei 50 % der Fälle mit Strabismus festgestellt worden. Was die andern Erkrankungen anbetrifft, so ist die Zahl nicht genügend gross, um Prozentuale feststellen zu können; es ist bedeutungsvoll, dass bei kindlichem Glaucomen, bei der angeborenem Ptosis und den kongenitalen Paralysen der Augenmuskeln normale Kurven gefunden worden sind, mit deutlichem pathologischen Vorwiegen bei den andern Fällen. Die elektroencephalographischen Veränderungen wurden durch kortikale Herde mit epileptischer Tätigkeit, Spitzenentladungen, diffuser Wellen und positiver Spitzen von 14–6 c/s. dargestellt. Geringere Veränderungen (Asymmetrie, schnelle Rhythmen, kleine Spitzen) wurden in einem kleiner Prozentsatz der Fälle von Strabismus gefunden.

Descubrimientos electroencefalográficos en el estrabismo concomitante y otras afecciones oculares.

Llevóse a cabo una investigación EEG en varias enfermedades oculares. Estrabismo en 80 casos, catarata congénita 10, glaucoma infantil 5, ptosis congénita 3, síndrome de Lawrence Moon Biedl 3, quératocono 1, parálisis ocular congénita 2. Los pacientes examinados fueron casi exclusivamente niños. Halláronse anomalías distintivamente reveladas por la EEG en un 50 % de casos de estrabismo. En cuanto concierne los demás síndromes, el número de sujetos examinados no fué suficiente para permitir establecer

un porcentaje. No obstante, se consignaron registraciones normales en los casos de glaucoma infantil, ptosis congénita y parálisis muscular ocular congénita. Las anomalías reveladas por la EEG, consistieron principalmente en elevaciones y ondas difusas y 14 y 6 descargas positivas afiladas y menos frecuentemente focos corticales epileptógenos. Anomalías menores (asimetrías, frecuencias rápidas o elevaciones agudas menores) han sido registradas en un pequeño porcentaje de casos.

References

1. Dyer, D. and Bierman, E. O.: Cortical potential change in ambliopia ex anopsia; A. Preliminary report. *Am. J. Ophthalm., 33:* 1095, 1950.
2. Fois, A. and Frezzotti, R.: Osservazioni elettroencefalografiche preliminari in alcune affezioni oculari, con particolare riguardo a quelle rapportabili a perturbamenti del sistema nervoso centrale. Atti della Accademia dei Fisiocritici: 1955.
3. Gibbs, E. L., Fois, A. and Gibbs, F. A.: The electroencephalogram in retrolental fibroplasia. *New England J. Med., 253:* 1102, 1955.
4. Hartman, E.: L'électroencephalogramme dans le glaucome. Acta XVII Concilium Ophthalmologicum 1954: 937. University of Toronto Press 1955.
5. Levina, L. and Neuschtadt, G. M.: Electrical activity of the brain in glaucoma, from *Excerpta Medica-Ophthalmology, 6:* 455, 1952.
6. Parsons-Smith, G.: Activity of the cerebral cortex in ambliopia. *Br. J. Ophthalmology, 37:* 359, 1953.
7. Steiger, R. M. and Wurth, A.: Die Fixation Photographie und die Electroencephalographie in der Burteilung der Schielambliopie. *Ophthalmologica, 129:* 240, 1955.
8. Stillerman, M. L., Gibbs, E. L. and Perlstein, A. M.: Electroencephalographic changes in strabismus. *Am. J. Ophtalm., 35:* 54, 1952.

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The Physiological Heart Murmur in Children

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If one compares auscultation of the heart in children with that in adults, a remarkable difference becomes apparent. The heart sounds in children are louder and more intense, depending to a great degree on the character of the chest wall and the position of the heart. It follows, therefore, that the examiner who is not acquainted with the findings on auscultation of the heart in children, will be surprised as to the wealth of the findings. This ability, "to hear better", introduces the great danger of overestimating these auscultatory findings. It is not uncommon for healthy children of any age to be invalidized on the basis of misinterpretation of the heart sounds. Such a situation may well lead to the development of neuroses. It is therefore of importance to be able to interpret correctly the heart sounds which are physiological. The work presented here is a phonocardiographic study of the heart sounds and murmurs in normal healthy children.

A systolic murmur is described in the literature under many different terms, the most common being "functional murmur" (1), "accidental murmur" (2), "innocent murmur" (3), "anorganic murmur" (4) and "nonpathological murmur" (5). Each of these expressions implies that the murmur arises in individuals with normal hearts. To a great extent, such murmurs have been observed in children during the usual stethoscopic examination. In most of the cases, the intensity of the murmur has been described as being weak compared with that of the heart sounds.

In many phonocardiographic examinations the physiological murmur has been recorded. McKee (6) mentioned that the systolic murmur occurs in 90 % of children with normal hearts between the ages of five and seventeen years. Mannheimer (7) reported the same phenomenon in 75 % of 135 children examined between one and fourteen years of age. Carlgren (8) stated that the frequency of such findings is 50 % between the ages of three and seventeen years. McKee has pointed out that the murmur was observed in the remaining 10 % as waves of low amplitude, and Mannheimer, in a later article (9) was of the opinion that the incidence of weak systolic murmurs in children examined with better methods of phonocardiographic technique, approached 100 %.

One characteristic common to all physiological murmurs is the position of the murmur in the cardiac cycle, i.e. in the first part of systole. Physiological diastolic murmurs have been recorded in a few cases in adults (4, 10, 11), but to our knowledge, at the present time, have not been described in normal children.

Technique

The examinations of this study, were made using a calibrated phonocardiograph, constructed according to Mannheimer and Stordal (7). This apparatus is now manufactured by the Elema Company, Stockholm.

The principle of calibrated phonocardiography may be briefly summarized, as follows:—

The apparatus is divided by filters into five channels with the nominal frequencies 25, 50, 100, 200 and 400 cycles per second. Thus, each nominal frequency is situated one octave from its neighbour. In the lower frequency channels, the low frequency heart sounds appear most clearly, whereas the higher frequency murmurs are better registered in the higher frequency channels. One filter which simulates the sensitivity curve of the ear (O-isophone, according to Fletcher) reproduces in a sixth channel an auditory registration of the sound phenomenon. A tube generator is built into the apparatus which regulates the unit of measurement of amplification of each channel, for example $\frac{1}{20}$, $\frac{1}{50}$, $\frac{1}{100}$. A dynamic microphone is employed.

Material

The material consisted of 108 children from one to fourteen years of age who had been examined at our Clinic during 1954. These children were considered normal after an examination that included clinical history, physical examination, electrocardiograms including chest leads, and in 88 cases X-ray examination of the heart. All children with any history or sign of rheumatic disease were excluded.

The distribution of the cases according to age and sex is shown in Table 1.

The 108 children were examined at rest in the recumbent position. The phonocardiographic recording was made in expiratory apnea so that the heart sounds could be most clearly recorded. As a rule, the microphone was placed over the apex, the second left and right intercostal spaces, and in addition, in other positions where indicated.

The intensity of the systolic murmur, the location of its maximal intensity, the position in the cardiac cycle and the character of the waves were determined. Measurement of the maximal amplitude of the murmur was made in the 200 cps. channel as the murmurs were usually most clearly recorded in this channel. The degree of amplification was $\frac{1}{50}$ in all recordings.

TABLE 1

Distribution of the cases according to age and sex.

No.	Age (years) 1–4	5–8	9–14	Total
Boys	13	23	20	56
Girls	10	25	17	52
Total	23	48	37	108

Results

In all of the 108 cases, systolic murmurs with an amplitude greater than 1 mm were recorded.

Fifty-one cases (47.2%) showed systolic murmurs with an amplitude less than 3 mm, and with an average amplitude of 2.1 mm. The murmurs were recorded with the same intensity at the apex as at the base, and did not show a definite point of maximal intensity. These weak murmurs were of short duration and were localized to the first two-thirds of systole. (Fig. 1.)

Fifty-seven cases (52.8%) had systolic murmurs with a greater amplitude than 3 mm. In this group, one could differentiate two distinct types of

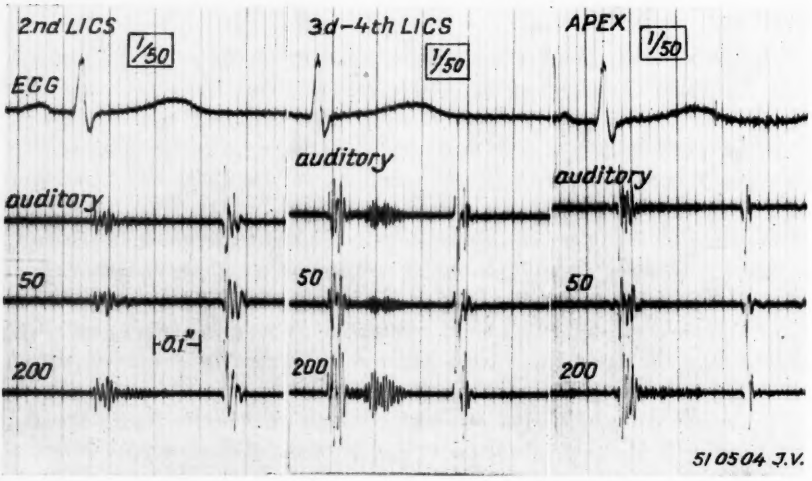

Fig. 1. Phonocardiogram, girl, 8 years, normal heart. Low amplitude systolic waves over 2nd RICS, 2nd LICS and apex. Boxed figures are a measurement of the degree of amplification. Other figures denote nominal frequencies of the channels.

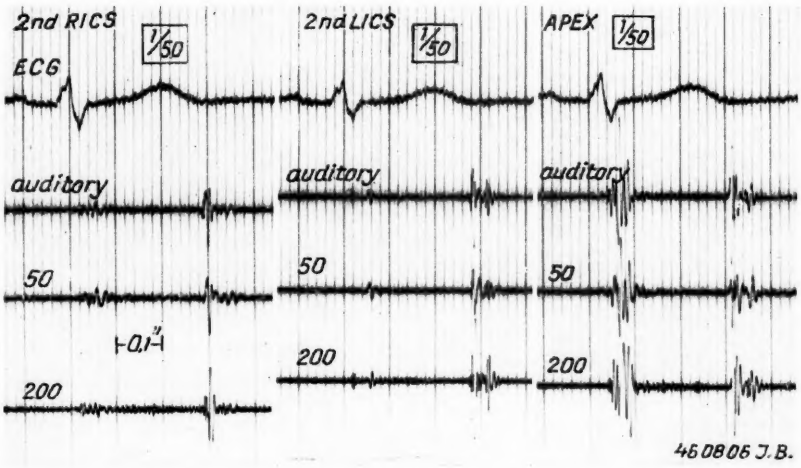

Fig. 2. Phonocardiogram, girl, 3½ years, normal heart. A sinus-shaped systolic murmur with point of maximal intensity clearly visible over 3rd and 4th LICS. Observe the interval between the first heart sound, and the murmur. Boxed figures are a measurement of the degree of amplification. Other figures denote nominal frequencies of the channels.

murmurs, with characteristic phonocardiographic patterns. Of these 57 cases with the stronger systolic sounds, 47 (43,5% of the total) showed a systolic murmur which clearly defined itself by regular waves of the same general frequency. We have called this murmur, the "sinus-shaped murmur" (Fig. 2). The average amplitude was 4.7 mm and in a few cases extended to 8 mm. The point of maximal intensity was well localized to a small area, the location of which over the precordium is shown as in Fig. 3. The sinus-shaped systolic murmur has a short duration, occupies only a part of systole, and is most intense just prior to mid-systole. The murmur is clearly separated from the first heart-sound by a short interval.

In the remaining 10 cases (9.3% of the total), the systolic murmur consisted of irregular waves which immediately followed the first heart sound and which occupied the first one-third of systole. The murmur was strongest early, and showed a decrescendo pattern. The average amplitude was 4.1 mm. In 9 of the 10 cases the murmur was recorded most intensely over the second left intercostal space.

The Influence of Heart Action on the Physiological Murmur

To investigate the influence of heart action on the strength and character of the physiological murmur, a group of 24 normal children between three and twelve years of age were examined with phonocardiography after the

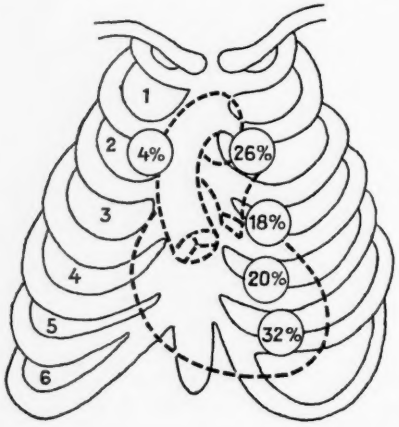

Fig. 3. Distribution of the location of maximal intensity of the sinus-shaped murmurs as to their position over the precordium.

inhalation of amyl nitrite, following the subcutaneous injection of dihydroergotamine, and after physical work.

The examinations were carried out according to the following schemes:—

1. After 15 minutes of rest in the recumbent position.
2. Immediately after physical work, which was performed on a cycle ergometer in the sitting position. The degree of work varied according to the child's age and size, and was between 200 kgm $\times$ 3 minutes, and 400 kgm $\times$ 6 minutes. The working performance was in response to a submaximal working load (12).
3. At the time of maximal facial flush following the inhalation of an ampoule of amyl nitrite.[1]
4. After the subcutaneous injection of 0.5 mg of dihydroergotamine.

Results

In 18 of the 24 children studied, faint systolic murmurs (similar to those illustrated in fig. 1) were recorded at rest. In 16 of these 18 cases, physical work produced a protosystolic murmur of decrescendo character with a maximal intensity over the second LICS (similar to the decrescendo murmur described above). The duration of systole (from the Q-wave of the ECG to the onset of the second heart sound) was shortened in all cases. Apart from this, however, the pulse frequency was remarkably slow and, in some cases, even less than at rest.

After inhalation of amyl nitrite, the amplitude of the protosystolic murmur increased to a greater degree than following work, and the systolic time was further shortened. (Fig. 4.)

[1] Burroughs Wellcome & Co. Amyl nitrite "Vaporole" 0,3 cc®.

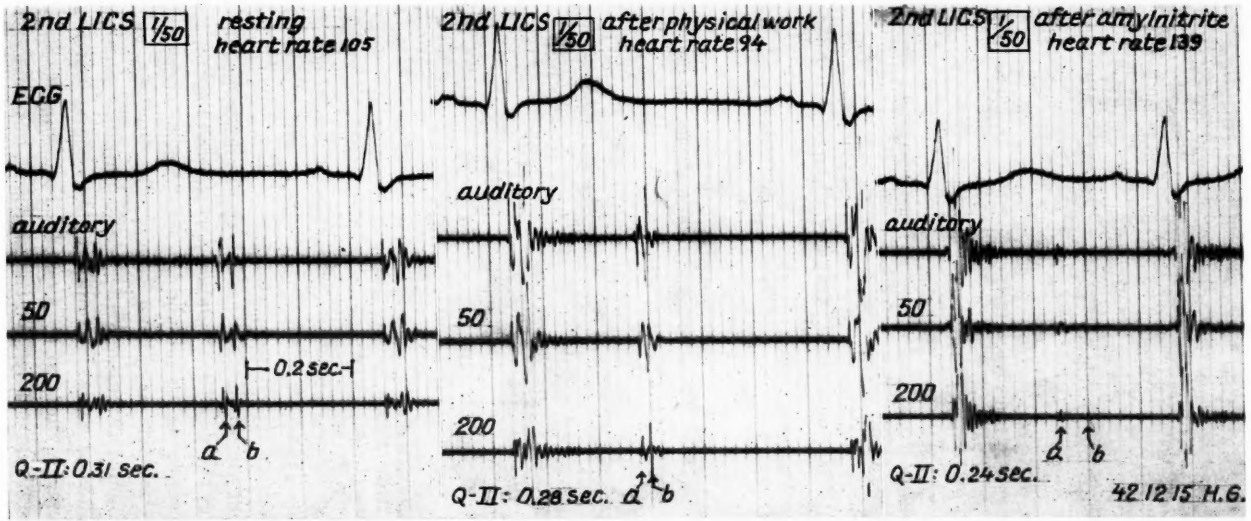

Fig. 4. Phonocardiogram, boy, 12 years, normal heart. Examination after rest, physical work, and amyl nitrite inhalation. Observe the increase in the intensity of the murmur, in relation to shortening of the systolic time. (Q-II = from the Q-wave of the ECG to the beginning of the second heart sound). There is a distinct variation, furthermore, in the splitting of the components of the second heart sound. *a* and *b*, aortic and pulmonary components of the second heart sound. Boxed figures are a measurement of the degree of amplification. Other figures denote nominal frequencies of the channels.

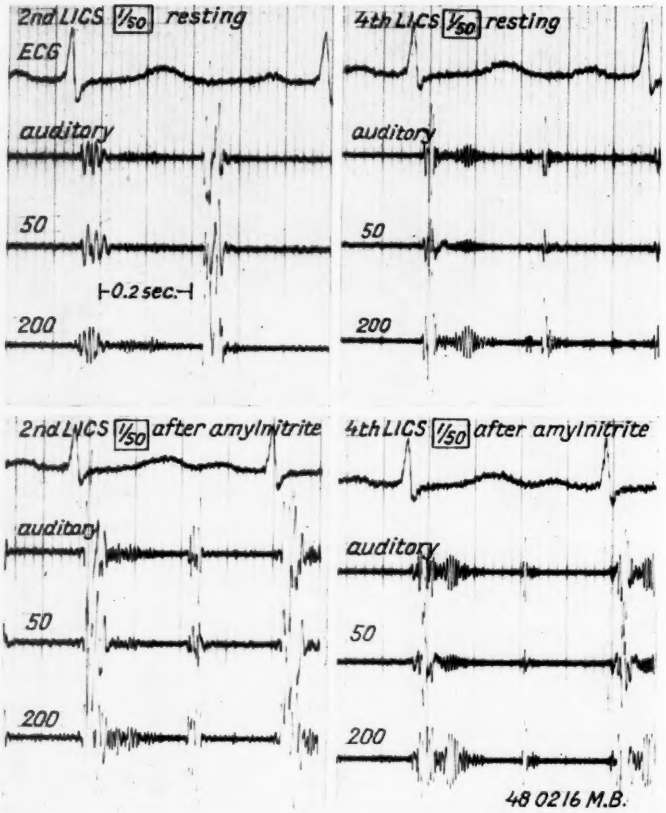

Fig. 5. Phonocardiogram, girl, 6 years, normal heart. Over the 2nd LICS, similar findings as in figure 4 are present. There is a physiological sinus-shaped murmur over the 4th LICS at rest, which increases in intensity following amyl nitrite without a change of the wave character, and which retains the interval between the murmur and the first heart sound. Boxed figures are a measurement of the degree of amplification. Other figures denote nominal frequencies of the channels.

One case, following the inhalation of amyl nitrite, developed a clear late systolic murmur over the 2nd LICS, and a short diastolic murmur over the 2nd RICS. A few minutes later, the phonocardiogram returned to normal. A repeated examination two days later, gave similar findings.

In 6 of the 24 children, a sinus-shaped systolic murmur was registered at rest. The murmur showed a maximal amplitude over the fourth and fifth left intercostal spaces, just medial to the apex. Following work, and after amyl nitrite, the amplitude of the murmurs increased, but the characteristic

waves, and the localization with a short interval following the first heart sound remained unchanged. (Fig. 5.) Waves of a protosystolic murmur and a weak sinus-shaped murmur were superimposed on recording from the second LICS.

In the first three cases studied, the subcutaneous injection of dihydroergotamine was not followed by any change in the phonocardiogram, and it was identical with that recorded at rest.

The heart sounds were also altered by changes in heart action. Following physical work, and also after amyl nitrite inhalation, the first heart sound showed a definite increase in amplitude, especially the recordings over the apex. The amplitude of the second heart sound slightly increased after work also, but showed a definite decrease following amyl nitrite inhalation (fall in blood pressure). In five of the children examined the second heart sound was clearly split over the second LICS. The splitting diminished after work, and increased after amylnitrite (Fig. 4).

Discussion

During the protosystolic phase of the heart cycle, the heart musculature and the bloodstream move at their greatest rate. The stroke volume of the ventricles is expelled with great rapidity out into the great vessels. In previous animal experiments (13) the origin of swirls in the proximal segments of the great vessels has been shown to be within this portion of the heart cycle (i.e. protosystole). The infundibulum of the right ventricle, which in children, especially, is often narrow and irregularly walled, and the pulmonary artery, which is relatively well developed, have been considered to give origin to turbulence, and from this, a protosystolic murmur over the second left intercostal space (14). We have observed the great similarity between this physiological murmur and the murmur which occurs in atrial septal defects (15). In atrial septal defects with a normal Q-T time, the passage of the increased blood volume of the right heart through the relatively narrow infundibulum is considered to give the murmur (16). A lowered peripheral resistance also, has been described as increasing the speed of expulsion, and therefore the protosystolic murmur originates over the pulmonary valve area in individuals with normal hearts (17).

The results of our own examination confirm the probability of this mechanism. Following physical work, the cardiac output increases in order to satisfy the greater oxygen need of the body. The systolic time in normal children following work is shorter than at rest, and the unchanged stroke volume must pass into the aorta and pulmonary artery within a shorter time interval (16). Following amyl nitrite inhalation, a marked peripheral vasodilatation

occurs, which results in a fall in blood pressure and an increase of the output. In both situations, a recordable protosystolic murmur develops which is much more intense than at rest, and which, based upon the position of the pulmonary artery with the chest wall, is recorded most clearly over the second LICS.

In a number of normal children, there occurs a markedly whistling type of murmur within the first portion of systole. Descriptions such as "twanging-string murmur" (18) and "precordial vibratory murmur" (19) ascribe to the probable origin of the murmur and wave character. In the series of normal children mentioned above, this murmur was recorded in 43.5% of the cases and the murmur was clearly differentiated from the protosystolic murmur over the second LICS by its sinus-shaped waves, and ints localization over the more apical areas. Even following physical work, and the inhalation of amyl nitrite the wave character of the murmur was unchanged, and it was separated by a short interval from the first heart sound.

It was of interest, furthermore, that as a rule one could separate phonocardiographically each of the described murmurs when overlying one another, as in the case of a sinus-shaped murmur, when protosystolic murmur was produced over the second LICS by physical work or the inhalation of amyl nitrite.

Summary

One hundred and eight children with normal hearts were investigated by means of calibrated phonocardiography. At rest, faint systolic murmurs were recorded in all cases. In over half of the cases, the systolic murmurs were so strong, that differentiation into two different types was possible. The sinus-shaped murmur appeared in 43.5 % of the cases, and was recorded most intensely over the third to fifth left intercostal spaces. A protosystolic decrescendo murmur with maximal intensity over the second left intercostal space was recorded in 9.3 % of the cases. Diastolic murmurs were not recorded.

In the second portion of the investigation, the influence of the heart action on physiological murmurs was studied. Twenty-four normal children were examined after rest, physical work, and the inhalation of amyl nitrite. This revealed, as a rule, that the faint systolic waves were replaced by a protosystolic decrescendo murmur following work and amyl nitrite inhalation. This was probably due to an increased ejection speed with an unchanged stroke volume and shortened systolic time. When a typical sinus-shaped murmur was noted at rest, the amplitude of the murmur was increased after work, as after amyl nitrite inhalation. In some cases, both of these murmurs could be found to overlie one another in the phonocardiogram after work.

Le bruit de souffle physiologique chez l'enfant.

Des examens à l'aide de phonocardiogrammes gradués ont été effectués sur cent et huit enfants dont le cœur était normal. Au repos, de légers souffles systoliques furent enregistrés dans tous les cas. Dans plus de la moitié des cas, les souffles systoliques étaient tellement forts qu'il fut possible d'établir une classification en deux

types différents. Un souffle sinusoïdal fut enregistré dans 43,5 % des cas, avec un maximum d'intensité au niveau des 3e, 4e et 5e espaces intercostaux gauches. Un souffle à decrescendo protosystolique atteignant son maximum d'intensité au niveau du 2e espace intercostal gauche fut enregistré dans 9,3 % des cas. Aucun souffle diastolique ne fut enregistré. La seconde partie de cette étude fut consacrée à l'examen des effets de l'activité cardiaque sur les souffles physiologiques. Vingt-quatre enfants normaux furent examinés : à la fin d'une période de repos, après un travail physique et après une inhalation de nitrite d'amyle. On a constaté qu'en règle générale, le travail et l'inhalation de nitrite d'amyle entraînaient l'apparition d'un souffle à decrescendo protosystolique venant se substituer aux légères ondes systoliques. Ce phénomène est probablement du à l'accélération de l'expulsion, le volume systolique étant resté inchangé tandis que la durée de la systole était raccourcie. Dans les cas ou l'on notait au repos un souffle sinusoïdal caractéristique, l'amplitude de ce souffle devint plus grande après le travail ainsi qu'après l'inhalation de nitrite d'amyle. Dans certains cas, un chevauchement de deux de ces souffles fut observé dans le phonocardiogramme enregistré après le travail.

Das physiologische Herzgeräusch bei Kindern.

108 herzgesunde Kinder wurden mit Hilfe der kalibrierten Phonokardiographie untersucht. Im Ruhezustand wurden schwache systolische Geräusche in allen Fällen registriert. Bei mehr als der Hälfte der Fälle waren die systolischen Geräusche so stark, dass eine Differenzierung in zwei verschiedene Typen möglich war. Das sinusförmige Geräusch erschien in 43,5 % der Fälle und wurde am stärksten über dem dritten bis zum fünften linken Interkostalraum registriert. Ein protosystolisches decrescendo Geräusch mit maximaler Intensität über dem zweiten linken interkostalen Raum wurde in 9,3 % der Fälle beobachtet. Diastolische Geräusche wurden nicht festgestellt. Im zweiten Teil der Arbeit wurde der Einfluss der Herzaktion auf die physiologischen Geräusche studiert. 24 normale Kinder wurden im Ruhezustand, nach physischer Arbeit und nach Inhalation von Amylnitrit untersucht. Es zeigte sich in der Regel, dass die schwachen systolischen Wellen nach physischer Arbeit und nach Amylnitritinhalation von einem protosystolischen decrescendo Geräusch abgelöst wurden. Dieses hing wahrscheinlich von einer erhöhten Auswurfgeschwindigkeit bei unverändertem Schlagvolumen und verkürzter Systolendauer, ab. Wenn ein typisches sinusförmiges Geräusch im Ruhezustand beobachtet wurde, so wies das Geräusch nach einer Arbeitsleistung oder nach Amylnitriteinatmung eine vergrösserte Amplitude auf. In einigen Fällen konnten nach einer Arbeitsleistung beide Geräusche über einander gelagert im Phonokardiogramm festgestellt werden.

Murmullo fisiológico cardíaco infantil.

Ciento y ocho niños cuyo corazón se presentaba normal, fueron sometidos a una investigación por medio de fonocardiografía calibrada. En situación de reposo, se registraron, en todos los casos, débiles murmullos sistólicos. En más de la mitad de los casos, los murmullos sistólicos se manifestaban con tanta fuerza, que fué posible diferenciarlos bajo dos tipos distintos. Un murmullo senomorfo apareció en el 43,5 por ciento de los casos, localizándose su mayor intensidad en los espacios intercostales tercero a quinto izquierdos. Se registró, en 9,3 por ciento de los casos, un murmullo protosistólico, en grado decrescendo, cuya máxima intensidad se localizaba en el segundo espacio intercostal izquierdo. No se registraron murmullos diastólicos. En la segunda porción de la investigación, se estudió la influencia de la acción cardíaca

sobre los murmullos fisiológicos. Veinticuatro niños normales fueron examinados respectivamente después de descanso, trabajo físico e inhalación de nitrito de amilo. Por regla general, esto reveló que las ondas sistólicas débiles, eran reemplazadas por un murmullo protosistólico en decrescendo después del trabajo y de la inhalación nitritoamílica. Probablemente esto dependía del aumento de la velocidad de expulsión, volumen inalterado y tiempo reducido de la sístole. Cuando, en situación de reposo, se notaba un típico murmullo senomorfo, la amplitud del murmullo, acusaba un aumento después del trabajo, así como después de la inhalación de nitrito de amilo. En algunos casos, pudo comprobarse que ambos murmullos referidos, se sobreponían el uno al otro en el fonocardiograma después del trabajo.

References

1. Luisada, A.: Heart. The Williams and Wilkins Company. Baltimore 1948.
2. Fanconi, G. and Wallgren, A.: Lehrbuch der Pädiatrie. B. Schwabe und Co. Basel 1950.
3. Evans, W.: Cardiology. Butterworth. London 1948.
4. Calo, A.: Les bruits du cœur et des vaisseaux. Masson et C^{ie} Paris 1950.
5. Harris, T. N.: Phonocardiographic study of pulmonic-systolic murmurs in children. *Am. Heart J., 50:* 805, 1955.
6. McKee, M. H.: Heart sounds in normal children. *Am. Heart J., 16:* 79, 1938.
7. Mannheimer, E.: Calibrated phonocardiography and electrocardiography. *Act. pæd., 28:* Suppl. *2*, 1940.
8. Carlgren, L. E.: Gallop rhythm in children. *Act. pæd., 33:* Suppl. *6*, 1946.
9. Mannheimer, E.: Fonokardiografi. *Svensk läkartidning, 51:* 2061, 1954.
10. Lian, C., Welti, J. J., Djordjevitch and Stefanovitch: Les souffles piaulants cardio-pulmonaires. *Arch. Mal. Cœur, 30:* 412–424, 1937.
11. Marchal, G.: Souffles diastoliques. *In:* Leçons de cardiologie faites à l'hôpital Broussais. 2^{e} série: 49–73 Paris, Doin 1938.
12. Wahlund, H.: Determination of the physical working capacity. *Act med. scandinav.*, Suppl. *215*, 1948.
13. Ceradini, G.: Il mecanismo delle valvole semilunari del cuore. *Gazz. med. italiana-lombarda*, 1871.
14. Tripier, R. and Devic: Sémiologie du cœur et des vaisseaux. Masson. Paris 1897.
15. Kjellberg, S. R. *et al.*: Diagnosis of Congenital Heart Disease. The Year Book Publishers Inc. Chicago 1955.
16. Jonsson, B.: Personal communication, 1956.
17. Spitzbarth, H.: Klinische Studien zur Entstehung der akzidentellen systolischen Geräusche über der Auskultationsstelle der Pulmonalisklappe. *Arch. für Kreislaufforschung, 22:* 1, 1955.
18. Still, G. H.: Common Disorders and Diseases in Childhood. 3rd ed. Oxford University Press, London 1918.
19. Harris, T. N. and Friedman, S.: Phonocardiographic differentiation of vibratory murmurs from those of valvular insufficiency. *Am. Heart J., 43:* 707, 1952.

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Favourable Effect of Liquid Formula-Feeding High in Fat to Coeliac Children

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In the treatment of coeliac disease the main principles of the dietary regimen is to exclude foodstuffs rich in roughage and substances capable of causing symptoms of intolerance, especially gluten. At the same time a satisfactory calorie level and an adequate supply of essential metabolites should be guaranteed. Such regimes usually consist of an ordinary diet with restriction of starch and fat (Andersen & di Sant'Agnese). It is, however, difficult to secure a satisfactory calorie supply with a low fat diet, and as yet it has never been proved that fat as such is injurious in coeliac disease. We therefore investigated the effect of an adequate formula feeding free from roughage and gluten and rich in fat. The results obtained were good both from a clinical point of view and with regard to the absorption of fat, when the latter was supplied in the form of corn oil. However, when corn oil was replaced by cream the absorption of fat was markedly decreased. In both cases the addition of products containing gluten produced symptoms of intolerance.

Experimental

The experimental series consisted of five children—two normal subjects (Cases I and II), two children with coeliac disease (Cases III and IV), and one child with cystic fibrosis of the pancreas (Case V); see Case Reports below.

Experimental diets

Two experimental diets described by Ahrens *et al.* were used. Here these diets are referred to as corn oil formula and cream formula. The composition is given in Table 1. The distribution of the calories was the same in both formulae, namely 15 per cent protein, 40 per cent fat and 45 per cent carbohydrates. The calorie content in both was 1.25 cal. per gram. The total daily amount of the formula was distributed over 4–5 meals.

TABLE 1

Composition of formulae supplied.

Diet formulae and ingredients	Weight (g)	Protein (g)	Fat (g)	Carbohydrate (g)
Cream formula				
Milk	100	3.3	4.0	5.0
Cream, 40 %	45	1.0	18.0	1.6
Skimmed milk powder	29	14.5	0.3	11.3
Dextrose	38	—	—	38.0
Water	188	—	—	—
Total	400	18.8	22.3	55.9
Corn oil formula				
Corn oil	21.9	—	21.9	—
Skimmed milk powder	37.5	18.8	0.4	14.7
Dextrose	41.5	—	—	41.5
Water	299	—	—	—
Total	400	18.8	22.3	56.2

Diet periods

The duration of the diet periods and the amount of fat supplied during each period are given in Tables 2 and 3. In those cases in which the periods did not follow one another immediately, the patient received the experimental diet under consideration for ½–1 week before and after the actual balance study period. The beginning and end of the period were marked with carmine. With the exception of Case III, every patient was studied for 2 diet periods, one with the corn oil formula and one with the cream formula. During these periods the patient received only water or lemonade beside the formula. In Case III the patient was studied for 8 different periods:

I. *Ordinary food.*—The fat was given mainly in the form of butter, cream and milk. The diet also contained about 25 g white bread per day and oat porridge corresponding to about 15 g of oat meal per day. The diet also included potatoes, fish, minced meat and eggs.

II. *Corn oil formula.*

III. *Cream formula.*

IV. *Corn oil formula.*

V. *Corn oil formula + food, rich in gluten.*—In addition to the formula, during this period the patient received white bread during the first 7 days of period in a quantity of 150 g per day and during the remaining days in an amount of 100 g per day.

VI. *Ordinary food, poor in gluten.*—During this period fat was supplied mainly in the form of milk. The diet also included eggs, fish, lean meat, potatoes and vegetables. Instead of bread and porridge the patient received rice crispies.

VII. *Ordinary food, rich in gluten.*—During this period fat was supplied in the form of butter and milk. The patient also received about 60 g white bread per day and porridge corresponding to about 20 g of oat meal per day. Otherwise the diet consisted of ordinary food.

VIII. *Corn oil formula + food rich in gluten.*—During this period the patient received fat mainly in the form of corn oil, but in addition 25 g butter per day. Otherwise the diet consisted of about 90 g white bread per day and porridge corresponding to about 20 g of oat meal per day.

Collection and analysis of the stools

The faeces were collected quantitatively and weighed for each 24 hours interval during the experimental periods. The fat content was determined according to the method of van de Kamer *et al.* In Case III analyses were made on every 24 hours sample, and in the other cases, on the total amount of faeces collected for 3 days.

Case Reports

Case I (*Normal Child*).—The child was a girl, aged 19 months, and weighing 11,300 g (birth weight 2650 g). She was the first child of healthy parents. She had received breast milk for the first 3 weeks, then citric acid milk for six months and then ordinary children's food. At one month of age she was admitted to the clinic for 3 weeks on account of a slight gastrointestinal infection. Since then she had not had any digestive trouble or abnormal stools. She was admitted to hospital for a slight infection of the upper respiratory tract, from which, however, she recovered within a few days after which fat balance studies were carried out. During these studies she was in a good general condition without intestinal disturbances.

Case II (*Normal Child*).—The child was a boy, aged 5 years, and weighing 16,700 g (birth weight 3260 g). He was the second child of healthy parents. The boy had never had any digestive trouble or abnormal stools. During the experimental periods he was in a good general condition and had no digestive trouble. At the time of the investigation he was under observation in the clinic because of enuresis.

Case III (*Coeliac Disease*).—The patient was a boy, aged 6 and a half years, and weighing 16,800 g (birth weight 4800 g). He was the seventh child of healthy parents. One sister died one month of age from unknown cause. All the other siblings were alive and healthy. The child was breast-fed for only 7 weeks and then given citric acid milk. Vitamins A and D had been given in prophylactic doses.

At about 8 months of age he began to pass large, grey, foul-smelling stools and to lose weight. He was admitted to hospital at the age of 13 months where he was treated for six months for assumed coeliac disease.

During the following years he is said to have been in a fairly good condition. The stools were practically normal except during infections of the respiratory tract, when

usually voluminous, greyish stools were passed. Similar stools were also passed after over-exertion. During the last few years, however, the stools had more or less always been loose, grey and foul-smelling. Apart from restriction of fat he had received a normal diet. The abdomen had always been large and prominent, and especially during the last few years this had troubled him fairly much. During the last few months he had felt tired and listless and occasionally complained of pain in the umbilical region.

On admission he was pale and emaciated, especially the arms and legs. He was somewhat small for his age (weight 16.8 kg, height 108 cm). The abdomen was large and prominent and it felt doughy on palpation, but no pathologic resistance could be felt, neither was the liver or the spleen palpable. Physical examination of the heart and lungs revealed no signs of a pathological condition. The stools were loose, grey, voluminous and offensive.

He had anemia with a red-cell count of 3.3 millions and a hemoglobin percentage of 41. The white-cell count was 3100 with a normal differential count. The glucose tolerance test showed a low and prolonged curve. The duodenal juice showed a normal trypsin content. The serum protein was normal with a normal electrophoretic distribution. Skeletal X-ray showed no signs of rickets. The serum alkaline phosphatases were 9 Bodansky Units, and the citric acid content 30 micrograms per 100 ml.

For his anaemia the patient received iron therapy both intramuscularly and orally, with a good result. In addition, throughout his stay in hospital he received a water soluble multivalent vitamin preparation. During diet period II a marked improvement was noted in his general condition (see below) which persisted with slight variation throughout his stay in hospital. On discharge, after having spent 4 months in hospital, he weighed about 21 kg and the abdomen was no longer distended.

Case IV (*Coeliac Disease*).—The patient was a girl, aged 3 years, and weighing 11,500 g (birth weight 2800 g). She was the second child of healthy parents. She had two healthy sisters. During the first half year of life she received an ordinary formula and then ordinary children's food. With the exception of the summer months she had received a daily prophylactic dose of vitamins A and D. The stools had been normal except when she had a cold, then they were loose. During the last few months she had passed large grey, foul-smelling stools. The abdomen had always been somewhat prominent, but during the last few weeks it had become more distended. Recently she had also been tired and listless.

On admission she was pale, but otherwise appeared to be in a good general condition. The abdomen was distended but no pathological resistance was palpable; neither could the liver nor spleen be felt. She had moderate anaemia with a haemoglobin content of 52 per cent and a red blood cell count of 3.8 millions. The calcium, phosphorus and alkaline phosphatases were within normal limits. The serum protein was 5.9 per cent. The glucose tolerance test gave a flat curve. The blood values responded favourably to iron therapy. During the experimental period with corn oil formula the stools were of practically normal appearance. On discharge she was in a good condition.

Case V (*Cystic Fibrosis of the Pancreas*).—The patient was a boy, aged 10 months, and weighing 7600 g (birth weight 2800 g). He was the first child of healthy parents. He had been breast-fed for 2 months and then received in addition a special formula. At 2 months of age he received supplementary orange juice and tomatoes. For one month he had also received Vitamins A and D in prophylactic doses. Since birth he had been troubled by a cough with abundant expectoration. The stools had always been frequent, loose and foul-smelling. He was first admitted to the clinic at the age of 3 months. He then weighed 2900 g and was thin, but otherwise in a good condition.

He had oedema of both legs. The stools were loose, mucous and foul-smelling. He had occasional attacks of cough both during the day-time and at night. He had moderate anaemia with a haemoglobin content of 55 per cent and a red cell count of 3 millions, whilst the white cell count was 15,000 with normal distribution. The serum protein was 3.6 per cent (2.1 per cent albumin and 1.5 per cent globulin), the N.P.N. was 37 mg/100 ml. Duodenal juice showed no trypsin. The glucose tolerance test gave a somewhat prolonged curve but of normal height. The calcium, phosphorus and alkaline phosphatases in the serum were within normal limits. Wasserman's test was negative. Chest X-ray showed a somewhat increased marking of the bronchial tree, especially in the base of the right lung. In hospital the boy received breast milk and citric acid milk prepared from skimmed milk and supplementary aminoacid preparation. He also received iron therapy, a water soluble multivalent vitamin preparation and penicillin in prophylactic doses. He was also given an enzyme preparation. During this treatment his general condition gradually improved, the oedema disappeared and the serum protein increased to normal level. The boy then spent some months at home, where he received the same treatment as in hospital. He was often troubled by cough, but the stools were fairly formed.

On admission the second time he was in a good general condition. The anaemia had disappeared, and the haemoglobin content was now 99 per cent and the red blood cell count 4.8 millions. Still no significant amount of trypsin could be demonstrated. The serum protein was now 6.5 per cent. During the experimental period the stools were somewhat looser than before, but otherwise he felt well.

Results

Fat absorption

The results of the fat balance studies are given in Tables 2 and 3.

In the two normal cases the absorption of fat lay within normal limits both during the cream formula and the corn oil formula periods. In both the absorption of fat was somewhat higher during the period they received the corn oil formula.

Table 2 also gives the fat absorption in two patients with steatorrhea. In the patient with coeliac disease (Case IV) the fat absorption was greater when he was on a corn oil formula, then on the cream formula. The figures for the fat absorption in per cent of intake for these periods were 88.7 and 79.6 respectively. The dietary fat per day during both periods was roughly the same, namely 44.0 and 45.2 g respectively. In the patient with cystic fibrosis of the pancreas (Case V) the absorption of fat was the same for both formulae.

Table 3 gives values for fat absorption in the other patient with coeliac disease (Case III). The following results were obtained for the different experimental periods.

Ordinary food (I) and ordinary food, rich in gluten (VII).—During period I the diet included foodstuffs containing gluten although not to the same extent as during period VII. During these 2 periods the fat was given in the

TABLE 2

Results of fat balance studies on cream formula and corn oil formula diets in Cases I, II, IV and V.

For details, see text.

Diet formula	Duration of the diet period (days)	Fat intake (g) Total	Fat intake (g) Daily	Faeces, wet weight, average daily value (g)	Faecal fat (g) Total	Faecal fat (g) Daily	Fat absorption Total (g)	Fat absorption Daily (g)	Fat absorption % of intake
				Case I (Normal Child), age 17 mo., weight 11.3 kg					
Cream	10	335	33.5	24.5	31.7	3.2	303	30.3	90.5
Corn oil	10	341	34.1	17.5	5.5	0.6	335	33.5	98.3
				Case II (Normal Child), age 5 yr., weight 16.7 kg					
Cream	10	669	66.9	41.8	50	5.0	619	61.9	92.5
Corn oil	11	558	50.7	29.5	18.4	1.7	540	49.1	96.5
				Case IV (Celiac Disease), age 3 yr., weight 11.5 kg					
Cream	9	407	45.2	35.4	83.3	9.2	324	36.0	79.6
Corn oil	9	396	44.0	27.1	45.3	5.3	351	39.0	88.7
				Case V (Cystic Fibrosis of the Pancreas), age 10 mo., weight 7.6 kg					
Cream	7	346	49.4	77.4	78.8	11.3	267	38.2	77.2
Corn oil	7	323	46.2	57.3	81.2	11.6	242	34.6	75.2

form of cream in a quantity of 58.3 and 56.1 g per day respectively. The absorption of fat as per cent of intake was 67.8 during period I and 71.7 during period VII.

Food rich in gluten + Corn oil formula (V and VIII).—During these experimental periods the diet was high in gluten. During period V fat was given only in the form of corn oil and during period VIII mainly as corn oil. The amounts supplied were 63.8 and 66.1 g, respectively, per day and the absorption as per cent of intake was 86.1 and 85.3 respectively.

It was thus apparent that in a a diet containing gluten, the fat was absorbed better when given in the form of corn oil (periods V and VIII) than when given in the form of cream (periods I and VII), despite the fact that the daily fat intake during the first two mentioned periods was about 15 per cent higher than during the latter two.

Ordinary food poor in gluten (VI).—During this period the absorption of fat was good (85.6 per cent). The fat supplied per day was, however, lower than during other periods namely 37.2 g per day. This fat was given as cream.

Corn oil formula (II and IV).—During these two periods fat was given

TABLE 3

Results of fat balance studies on various diets in Case III.

Age 6½ years, weight 16,800 g. For details, see text.

Diet period and its duration (days)	Fat intake (g) Total	Daily	Faeces, wet weight, average daily value (g)	Faecal fat (g) Total	Daily	Fat absorption Total (g)	Daily (g)	% of intake
I (*Ordinary food*)								
11	641	58.3	135.0	206.0	18.8	435	39.5	67.8
II (*Corn oil formula*)								
25	2043	81.7	55.2	185.2	7.4	1858	74.3	91.3
III (*Cream formula*)								
14	803	57.3	97.5	191.3	13.7	612	43.7	76.2
IV (*Corn oil formula*)								
7	535	76.4	37.1	40.7	5.8	494	70.6	92.4
V (*Corn oil formula + food, rich in gluten*)								
14	893	63.8	79.3	123.3	8.8	769	55.0	86.1
VI (*Ordinary food, poor in gluten*)								
10	372	37.2	97.3	53.0	5.3	319	31.9	85.8
VII (*Ordinary food, rich in gluten*)								
14	786	56.1	163.6	221.7	15.8	564	40.3	71.7
VIII (*Corn oil formula + food, rich in gluten*)								
10	661	66.1	98.9	96.5	9.7	564	56.4	85.3

only in the form of corn oil. The amount of fat supplied was large, namely 81.7 and 76.4 g per day, respectively. The absorption of fat as per cent of intake was nevertheless high, namely 91.3 and 92.4 per cent, respectively.

Corn oil when supplied by itself, i.e. without other foodstuffs (periods II and IV), is thus absorbed better than corn oil given together with a diet containing gluten (periods V and VIII). The absorption of fat in per cent of intake during these experimental periods was 91.3 and 92.4, and 86.1 and 85.3, respectively. The fat intake per day was 10 per cent higher during the two first mentioned periods than during the last two.

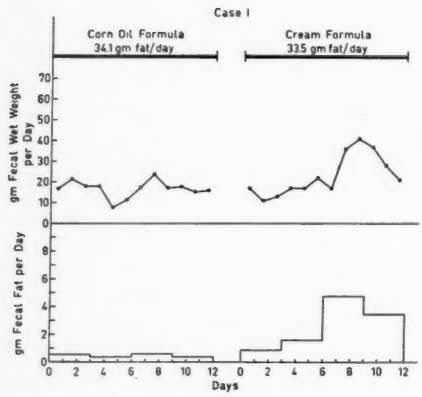


Fig. 1 (*left*). Faecal fat (3 days' average) and faecal wet weight (3 days' sliding means) in a normal child on corn oil formula and cream formula diets. Case I: girl, age 19 months, weight 11,300 g.

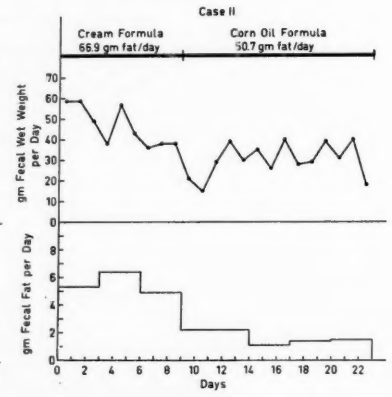


Fig. 2 (*right*). Faecal fat (3 days' average) and faecal wet weight (3 days' sliding means) in a normal child on cream formula and corn oil formula diets. Case II: boy age 5 years, weight 16,700 g.

Cream formula (*III*).—During this period fat was given exclusively in the form of cream. The fat intake was 57.3 g per day and of this, 76.2 per cent was absorbed.

It was found that cream given without other foodstuffs (period III) was absorbed better than when given together with foodstuffs containing gluten (periods I and VII). The absorption of fat in per cent of intake was thus 76.2 during period III and 67.8 and 71.7 during periods I and VII. The fat intake per day during these periods was practically the same (57.3, 58.1 and 56.1 g).

During periods II, III and IV the diet consisted exclusively of the respective formulae. On comparison between these groups, we see that fat when given in the form of corn oil (periods II and IV) was absorbed better than when supplied in the form of cream (period III). During the first-mentioned periods the fat intake was about 25 per cent larger per day than during the latter.

Faecal fat and appearances of the faeces

In the two normal cases the appearance of the faeces was normal both when the children were on the cream formula and on the corn oil formula. During the latter period, however, the faecal fat was significantly lower than during the former (Figs. 1 and 2); during these periods the amount

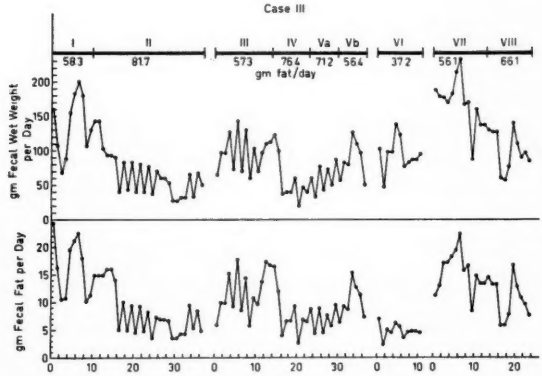


Fig. 3. Faecal fat and faecal wet weight (both 3 days' sliding means) in a patient with coeliac disease on various diets. For details, see text. Case III: boy, age 6½ years, weight 16,800 g.

of faecal fat per day in Case I was 0.6 and 3.2 g respectively, and 1.7 and 5.0 g respectively in Case II. Also the amount of faeces (wet weight) was smaller during the corn oil period.

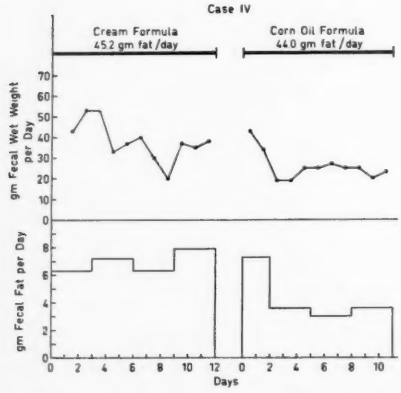
Fig. 5 gives the faecal determinations for the patient with pancreatic fibrosis (Case V). It is clear that the amount of faecal fat was the same for both formulae, namely about 11.5 g per day. The amount of faeces (wet weight) was, however, somewhat lower during the corn oil period.

Figs. 3 and 4 give the faecal determinations for the two patients with coeliac disease. In Case IV (Fig. 4) the amount of faecal fat during the corn oil period was barely half of that during the cream period, namely 5.3 and 9.2 g. During the corn oil period the appearance of the faeces also improved and they were of almost normal consistence. The amount of faeces (wet weight) was, however, only slightly lower during this period than during the cream formula period.

Data on the faeces for the other coeliac patient (Case III) are given in Fig. 3. The following results were obtained for the different dietary periods.

Ordinary food (*I*).—During this period the faeces were of typical coeliac appearance: foul-smelling, grey and semifluid. The amount of faecal matter passed was large and on the average 135 g daily (wet weight). During this period the faeces contained about 18.8 g fat daily.

Corn oil formula (*II*).—During this period a marked improvement was noted in the general condition of the patient. The abdominal distension decreased and at the end of the period it had almost disappeared. During this period the patient absorbed as much as 74.3 g of fat per day. The appearance of the faeces also improved and after about 14 days they were of normal colour and consistence. The faecal matter excreted per day decreased and was on the average 55 g (wet weight). The amount of fat in the faeces during this period was about 7.4 g per day.



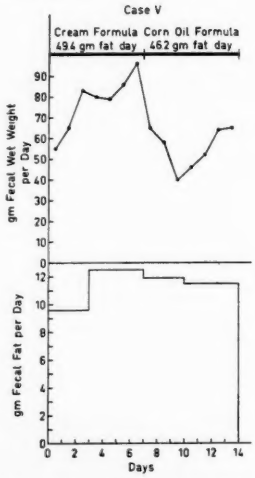


Fig. 4 (*left*). Faecal fat (3 days' average) and faecal wet weight (3 days' sliding means) in a patient with coeliac disease on cream formula and corn oil formula diets. Case IV: girl, age 3 years, weight 11,500 g.

Fig. 5 (*right*). Faecal fat (3 days' average) and faecal wet weight (3 days' sliding means) in a patient with cystic fibrosis of the pancreas on cream formula and corn oil formula diets. Case V: boy, age 10 months, weight 7600 g.

Cream formula (*III*).—During this period the faeces again showed a coeliac appearance, although not so pronounced as during period I. The faecal matter excreted was on the average 97 g per day (wet weight). The amount of fat in the faeces was about twice as much as during the previous period—13.7 g/day.

Corn oil formula (*IV*).—The appearance of the faeces was again normal and the amount excreted decreased to 37 g daily (wet weight). The amount of fat in the faeces decreased to 5.8 g per day.

Corn oil formula + food rich in gluten (*V*).—During this period the stools were on the whole normal, but towards the end of the period the patient developed intolerance symptoms in the form of nausea, abdominal discomfort and anorexia. The amount of faeces increased to 79 g daily (wet weight). The amount of fat in the faeces during this period was 8.8 g per day.

Ordinary food poor in gluten (*VI*).—During this period the amount of faeces was 87 g daily (wet weight), and the faeces contained about 5 g fat daily.

Ordinary food rich in gluten (*VII*).—During this period the stools again developed a coeliac appearance. More faecal matter was excreted than during any earlier period, namely 164 g daily (wet weight). The amount of fat in the faeces increased during this period from 5.3 to 15.8 g per day.

Corn oil formula + food rich in gluten (VIII).—During this period the appearance of the stools changed towards normal. The amount of faecal matter discharged decreased to 99 g daily (wet weight) and the faecal fat to 9.7 g per day.

Discussion

Treatment of coeliac children with a gluten-free formula free from roughage and rich in fat in the form of corn oil soon produced clinical improvement and a decrease in the faecal fat. This treatment appears to be more effective than the gluten-free normal diet now widely used. A striking effect of this treatment was the disappearance of the abdominal distension. Treatment with starch-free normal diet also decreases this symptom "but not to any greater extent" (Sheldon). When corn oil was replaced by cream steatorrhea recurred, but no deterioration was observed in the clinical picture. It is, however, possible that the replacement of the corn oil by the cream was not long enough for other symptoms to develop.

In the discussion of the cause of the favourable effect of the corn oil on children with coeliac disease it should be born in mind that even in the normal subjects corn-oil fat was more readily absorbed than cream fat. Comparison of the composition of these two fats (Table 4) (Baughman & Jamieson) shows in principle two differences; cream fat contains more saturated and less essential fatty acids. In investigations of the fat metabolism in normal infants Holt *et al.* found the rate of absorption of fat to be inversely proportional to the degree of saturation of the fatty acids in the dietary fat. This tendency to less good absorption of saturated fatty acids in normals, which was also found in our two normal cases appears to be more accentuated in coeliac disease. Thus Weijers & Van De Kamer, who studied the content of saturated and unsaturated fatty acids in faeces of coeliac patients on a

TABLE 4

Component fatty acid in corn oil and cream fat.

The figures given are per cent of total fatty acids.

Fatty acid	Corn oil	Cream fat
C_4–C_{12}	—	12.5–19
Myristic	—	5 –14
Palmitic	7.7	25 –35
Stearic	3.5	10 –15
Oleic	45.4	20 –30
Linoleic	40.9	0.5– 2
Arachidonic	0.4	—

gluten-free diet, found that oleic acid was absorbed to about 95 per cent, while more saturated fat in the diet produced an increase in the amount of saturated fatty acids in the faeces.

It is thus evident that in coeliac disease the fat absorption is disturbed even in the absence of gluten in the diet, a disturbance mainly of the absorption of the dietary saturated fatty acids.

The now widely accepted opinion of the significance of gluten in the etiology and treatment of coeliac disease is confirmed by the results of balance studies in Case III. In all of the dietary plans the addition of gluten impaired the absorption of fat. Thus corn oil fat has no protective effect against the influence of gluten. The difference in fat absorption between corn oil and cream in coeliac patients on a gluten-free diet is probably more marked when gluten is included in the diet. Thus Weijers & Van De Kamer (l.c.) found that when gluten was added to the diet of coeliac patients, a larger amount of saturated fatty acids was excreted with the faeces while the content of the unsaturated fatty acids was unchanged. This led these authors to the conclusion that the increased excretion of saturated fatty acids by coeliac patients is due in part to a disturbance in the intermediary fat digestion. That the excretion of fat in the intestines does not play such an important role as assumed by Weijers & Van De Kamer (l.c.), is, however, apparent from the results later obtained by Blomstrand & Lindquist and Bergström & Blomstrand with C^{13}-labelled fat. These authors showed a definite transformation of unsaturated fatty acids to saturated during digestion.

The favourable effect of the liquid formula containing corn oil on coeliac patients in this investigation must therefore be ascribed primarily to the complete absence of any gluten in the diet, secondly to the high content of unsaturated fatty acids in the corn oil, which are well absorbed by these patients. It is not yet possible to state whether the high content of essential fatty acids, chiefly linoleic acid, in the corn oil is of any special importance.

In patients with pancreatic fibrosis replacement of dietary cream by corn oil had no demonstrable effect on the fat absorption. This can be explained by the fact that patients with pancreatic fibrosis lack enzymes of importance for the absorption of corn oil as well as of cream.

Summary

Fat balance studies were carried out on children receiving a liquid formula diet containing fat either as corn oil or as cream. Fat represented 40 per cent of the total calorie supply.

In two normal subjects the fat absorption was within a normal range when they were on the corn oil formula as well as on the cream formula, the absorption of fat in per cent of intake being somewhat higher when they were on the corn oil containing diet.

In two children with coeliac disease the fat absorption was decreased as long as they were on the cream formula but practically normal when they received the corn oil formula. The faecal fat was about twice as high during the former dietary period as during the latter. Addition of gluten-containing foodstuffs to both formulae produced an equal increase in the faecal fat. During the corn oil diet period the children showed good clinical improvement.

The better absorption of fat from corn oil than from cream is probably attributable to the fact that corn oil contains a larger proportion of unsaturated fatty acids.

Effets favorables d'un régime liquide riche en graisses sur des enfants atteints de maladie coeliaque.

Des études du métabolisme des graisses ont été effectuées chez des enfants soumis à un régime liquide additionné de graisses sous forme d'huile de maïs ou de crême. Ces graisses représentaient 40 % de la teneur totale des aliments en calories. Chez deux enfants bien portants, la résorption des graisses fut normale aussi bien pour le régime à base d'huile de maïs que pour le régime à base de crême; cependant, le pourcentage de résorption des graisses par rapport aux quantités ingérées fut légèrement plus élevé avec l'huile de maïs. Chez deux enfants atteints de maladie coeliaque, la résorption des graisses fut inférieure à la normale aussi longtemps qu'ils reçurent le régime à base de crême, mais elle fut pratiquement normale lorsqu'on leur donna le régime à base d'huile de maïs. Les quantités de graisses retrouvées dans les fèces furent environ deux fois plus importantes avec le premier régime qu'avec le second. L'addition d'aliments renfermant du gluten aux deux régimes fut suivie d'une augmentation équivalente de la teneur des matières fécales en graisses dans les deux cas. Une bonne amélioration clinique fut observée chez ces enfants durant les périodes pendant lesquelles le régime à base d'huile de maïs fut appliqué. La meilleure résorption des graisses à partir de l'huile de maïs par rapport à celle qui fut observée avec la crême doit probablement être attribuée au fait que l'huile de maïs renferme une proportion plus importante d'acides gras non-saturés.

Günstige Resultate bei nach der flüssigen fettreichen Diätvorschrift ernährten Kindern mit Coeliakie.

Fettbilanzstudien wurden bei Kindern, die nach einer flüssigen Fette in der Form von Maisöl oder Sahne enthaltenden Diätvorschrift ernährt wurden, durchgeführt. Fett stellte 40 % der gesamten Kalorienzufuhr dar. Bei zwei normalen Kindern verblieb die Fettabsorption innerhalb normaler Grenzen, gleichgültig ob sie nach dem Maisöl- oder nach dem Sahnenrezept ernährt wurden, wobei die Absorption von Fett in Prozenten der Aufnahme bei der Maisöldiät ein wenig höher war. Bei zwei Kindern mit Coeliakie war die Fettabsorption herabgesetzt solange sie nach dem Sahnenrezept ernährt wurden, aber wurde annähernd normal, wenn sie sich auf die Maisöldiät umstellten. Der Fettgehalt im Stuhl war ungefähr doppelt so gross bei der ersteren als bei der letzteren Diät. Der Zusatz von Gluten enthaltenden Nährstoffen zu jeder der beiden Diätvorschriften führte zu einem gleichmässigen Anstieg der Fettausscheidung im Stuhl. Während der Maisöldiät wiesen die Kinder eine gute Besserung in ihrem klinischen Verhalten auf. Die bessere Absorption von Maisölfett im Vergleich zum Sahnenfett ist wahrscheinlich der Tatsache zuzuschreiben, dass Maisöl einen grösseren Anteil ungesättigter Fettsäuren enthält.

Efecto favorable de una fórmula alimenticia líquida altamente adípica en ninos afectos de celiaquía.

Se ha estudiado el balance adípico de niños sometidos a dieta de formulación líquida, conteniendo grasa, bajo forma de aceite de maíz o nata. La grasa representó un 40 por ciento de la totalidad de calorías suministradas. En dos sujetos normales, se redujo la liporesorción a lo normal, tanto al tratarse de la formulación con aceite de maíz, como de nata, resultando la liporsorción, en porcentaje de ingreso, algo más elevada en el caso de la dieta conteniendo aceite de maíz. En dos niños enfermos de celiaquía, la liporesorción disminuyó mientras durara la administración de la formulación de nata, pero fué prácticamente normal cuando se les suministró la de aceite de maíz. La grasa fecal era aproximadamente dos veces más elevada en el primer período dietético mencionado, que en el último referido. La adición de productos alimenticios, conteniendo gluten, a ambas fórmulas, produjo igual aumento de grasa fecal. Durante el régimen con aceite de maíz, los niños presentaron un buen mejoramiento clínico. La liporesorción, a partir del aceite de maíz, mejor que la de la nata, puede probablemente atribuirse al hecho de que el aceite de maíz contiene mayor proporción de ácidos grasos no saturados.

References

AHRENS, E. H., Jr., DOLE, V. P. and BLANKENHORN, D. H.: The use of orally-fed liquid formulas in metabolic studies. *Am. J. Clin. Nutrit., 2:* H. 5: 336, 1954.

ANDERSEN, D. H. and DI SANT'ANGNESE, P. A.: The celiac syndrome. *In* Brenneman, Practice of Pediatrics, Vol. I, Chapter 29.

BAUGHMAN, W. F. and JAMIESON, G. S.: Composition of corn oil. *J. Am. Chem. Soc., 43:* 2696, 1921.

BERGSTRÖM, S. and BLOMSTRAND, R.: Studies on the intestinal absorption of fat in man with the aid of labelled oleic and palmitic acid. *In* Biochemical Problem of Lipids. Butterworths Schientific Publications, London 1956, p. 323.

BLOMSTRAND, R. and LINDQUIST, B.: The intestinal absorption of carbon-labelled oleic acid in the normal infant and in congenital bile duct atresia. *Helvet. Ped. Acta, 10:* 627, 1955.

BLOMSTRAND, R. and LINDQUIST, B.: The intestinal absorption of carbon-labelled oleic and palmitic acid in the normal infant and in cystic fibrosis of the pancreas. *Helvet. Ped. Acta, 10:* 640, 1955.

HOLT, E. Jr., TIDWELL, H. C., KIRK, C. M., CROSS, D. M. and NEALE, S.: Studies in fat metabolism. I. Fat absorption in normal infants. *J. Pediat., 6:* 427, 1935.

KAMER, J. H. VAN DE, BOKKEL HUINIK, H. TEN, and WEIJERS, H. A.: Rapid method for the determination of fat in feces. *J. Biol. Chem., 117:* 347, 1949.

SHELDON, W.: Coeliac disease: a relation between dietary starch and fat absorption. *Arch. Dis. Childh., 24:* 81, 1949.

WEIJERS, H. A. and VAN DE KAMER, J. H., Coeliac disease. III: Excretion of unsaturated and saturated fatty acids by patients with coeliac disease. *Acta pædiat., 42:* 97, 1953.

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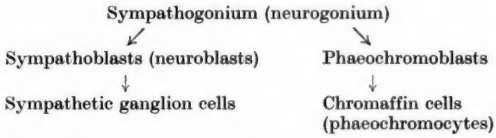
Phaeochromocytoma in a Six Year Old Girl

by MARGRETHE WEHN

It is a well-known fact that the embryonal sympathetic nervous tissue is not rarely the origin of tumours in children. According to Selye the earliest stage—the sympathogonium—under continued differentiation develops in two directions, partly through the sympathoblast to the fully developed sympathetic ganglion cell, and partly through the phaeochromoblast to the chromaffin cell or the phaeochromocyte as follows:



Tumours originated at the various stages of development are known under the designations sympathogonioma or neurogonomia, and further the sympathoblastoma or neuroblastoma, both malignant. From the differentiated ganglion cell the ganglion neurinoma is recognized as a rare, usually benign tumour. Tumours from the chromaffin cells are called chromaffinomas or phaeochromocytomas due to affinity of the cells to chromium salts, which stain them yellowish brown. These tumours may occur everywhere in the organism where chromaffin tissue is present, for preference in the medulla of the suprarenal glands, but also in sympathetic ganglia along the aorta, possibly intrathoracically. Such tumours have also been found in the carotid gland and even intracerebrally.

The phaeochromocytoma falls into a special class because the clinical picture is dominated completely by the hormonal pressor substances adrenalin and noradrenalin, produced by the tumour cells.

The lesion was described first in 1922 by Labbé and coworkers, subsequently several hundreds of cases in adults have been reported, the tumour most frequently occurring in the age group 30–50 years. The lesion is rare in children. In a publication from February 1956 Moore and coworkers record 24 cases—the total number known so far—in children under 14 years of age. Only six of these patients were below 10 years of age. Robinson & Williams (1956) give an account of a further two cases in boys of 8 and 10 years respectively.

The lesion appears to be fatal in children, if left untreated. In recent years, however, resources have been put at our disposal which are of decisive importance for diagnosis as well as for therapy, and thus also for the prognosis.

An account will be given here of a case of phaeochromocytoma in a six year old girl, which is illustrative of this.

Case report. — The family of the patient was healthy, and she had developed in a satisfactory way, psychically as well as somatically. The lesion in question commenced just after New Year 1956, when the parents noticed that the patient lost weight and became pale. Her appetite was very good all the time, and she drank strikingly much. Attacks of pain occurred in the stomach, throat and back of neck. Initially these attacks were mild and of brief duration, but subsequently they became more severe and more frequent. They occurred particularly in the morning, and when she came out in the cold. They had no connexion, however, with physical exertion or psychical affect. The pain was accompanied by nausea, but no vomiting. She grew lax and irritable, and had considerable constipation. The parents noticed fits of sweating without relation to pain. She often complained of feeling too hot. The mother gives the following graphic account of the dramatical development of the morbid picture in the course of two months: "We saw her actually wilting as the weeks went by, and many times I worded it like this: it looks as if she perishes bit by bit in our midst."

On March 6th 1956, two months after the onset of the symptoms, she was admitted into a provincial hospital under the diagnosis constipation and loss of weight. Two days afterwards she had an attack of abdominal pain, nearly collapsing, was pale, sweated, and vomited. Repeated blood pressure measurements showed increased values to about 150/100. Next day she had another attack with loss of consciousness. In the first and second fingers of the left hand jerks occurred, which grew into general clonic spasms, most pronounced on the left side. She had twitchings around the left eye and the left corner of the mouth, as also nystagmoid motions to the left. She was given luminal intramuscularly without effect, thereupon ether on open mask, and the spasms ceased after having lasted for one hour and a quarter.

Among other examinations two electroencephalograms were recorded, both showing a predominating slow activity with high potentials. The last, taken while the patient was awake, also showed signs of focal changes over the right hemisphere. The diagnoses phaeochromocytoma, encephalitis, and epilepsy, were considered, but due to the above-mentioned findings she appeared particularly suspect of intracranial expansive process, and on March 16th she was referred to the University Hospital, Department of Neurosurgery.

On admission, while the abdomen was palpated, she had an attack of pain accompanied by increase of blood pressure to 210/180. Under suspicion of phaeochromocytoma she was referred the same day to the Paediatric Clinic.

On examination in our department we found an exceedingly thin girl in miserable condition, greatly distressed. Her psychical status was very striking with staring eyes, she did not answer when addressed, but was orientated, such as being able to comply with requests to sit up, open the mouth, and so forth. On closer examination, however, e.g. blood pressure measurement, she resisted violently with yells and kicking.

At ten minute intervals she had attacks during which she threw herself wailing back and forth in bed. She had the appearance of being quite demented. After the

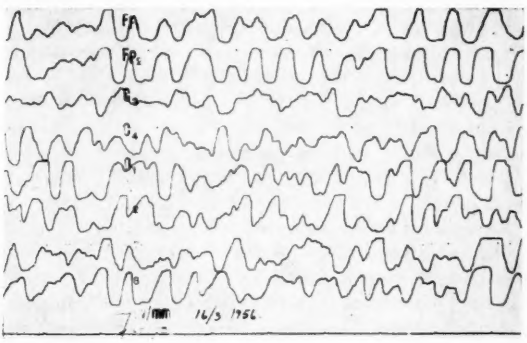


Fig. 1.
EEG before treatment.

attacks she stated that the pain had been localized alternatingly to stomach, throat and eyes. She was strikingly pale in the face while the skin on the distal parts of the limbs was coarsely patterned, strongly bluish, mottled and cold. Occasionally drops of sweat were seen on her face. She felt hot and constantly kicked off the bed clothes, but was afebrile. There was persistent tachycardia around 150 per minute. Blood pressure measured repeatedly on upper as well as lower limbs, showed hypertension, maximally 230/180, minimally 165/155. In the abdomen scybala were palpated in spastic intestines. No definite tumour was palpated in the renal regions. Firm palpation was avoided for fear of possible elevation of the blood pressure. It was difficult to evaluate the reflex conditions, but they showed nothing definitely pathological. Ophthalmoscopy demonstrated somewhat thin arteries, but no retinopathy.

Among other prominent positive findings was hypochloraemia about 80 milli-equivalents, in spite of non-vomiting and with ample intake of salt. There was no concurrent increase of the potassium values. Fasting blood sugar was 140 mg per cent. Electroencephalogram recorded when the patient was awake, demonstrated an exceedingly pathological picture (Fig. 1) with very irregular background activity consisting of delta waves characterized by slow frequency and high potentials. No definite focal signs were registered.

The regitin test showed positive reaction, with a maximal fall in systolic blood pressure of 90 mm and diastolic blood pressure of 80 mm Hg (Fig. 2).

A sample of urine was forwarded to Professor v. Euler in Stockholm after having been made acid to pH 3. The analysis showed secretion of 2,060 micrograms of noradre-

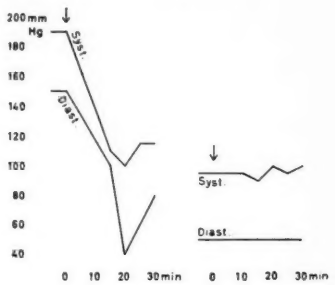


Fig. 2. *Regitin test.*
Left side—before treatment. A sharp fall is seen in systolic as well as diastolic blood pressure.
Right side—after treatment. No effect on blood pressure.
Arrows indicate time when 5 mg regitin is given intramuscularly

nalin and 7.5 micrograms of adrenalin in twenty-four hours. Normal values lie below 50 micrograms. This result showed that an adrenalin-producing phaeochromocytoma was present. With the diagnosis definitely established it was not considered advisable to perform urography or perirenal pneumography in order to locate the tumour, so as not to provoke hypertensive crises, and because the surgeon at any rate would secure a survey of both suprarenal glands. Electrocardiogram showed flattening of T_1 and T_3. X-ray of the heart was normal. The basal metabolism could not be recorded due to her wretched condition, and neither was it possible to obtain urea clearance values or sugar tolerance curve.

In accordance with the above findings preoperative treatment with regitin was planned. The use of adrenolytic substances was introduced by Goldenberg in 1947. He used piperoxan. In 1949 Grimson described the diagnostic use of regitin and drew attention to the value of preoperative peroral ingestion of the same agent. The effect is caused by a transitory diminution of the pressor effect of adrenalin and noradrenalin. Regitin is easily administered, involving only negligible by-effects such as drowsiness, palpitations and erythema. We made trials under constant checking of blood pressure, and with a dosage of 20 mg perorally every second hour, we succeeded in keeping the blood pressure about 140/100. There was a striking improvement during this medication. The fits of pain ceased, and the peripheral vascular symptoms subsided. Simultaneously she developed a transitory exanthema.

After premedication for five days she was referred to the Department of Surgery, where laparotomy was carried out. The left suprarenal gland was found to be normal, and no tumours were palpated along the vessels. The enlarged right suprarenal gland was removed without difficulty. The tumour was of the size of a chicken egg, with a thin edge of cortex on the one side, the remainder consisted of tumour tissue. The blood pressure was checked carefully during the operation, and showed slight variations. After removal of the tumour she was given continuous noradrenalin drip intravenously. This was discontinued after thirty-six hours. The post-operative course was perfectly satisfactory.

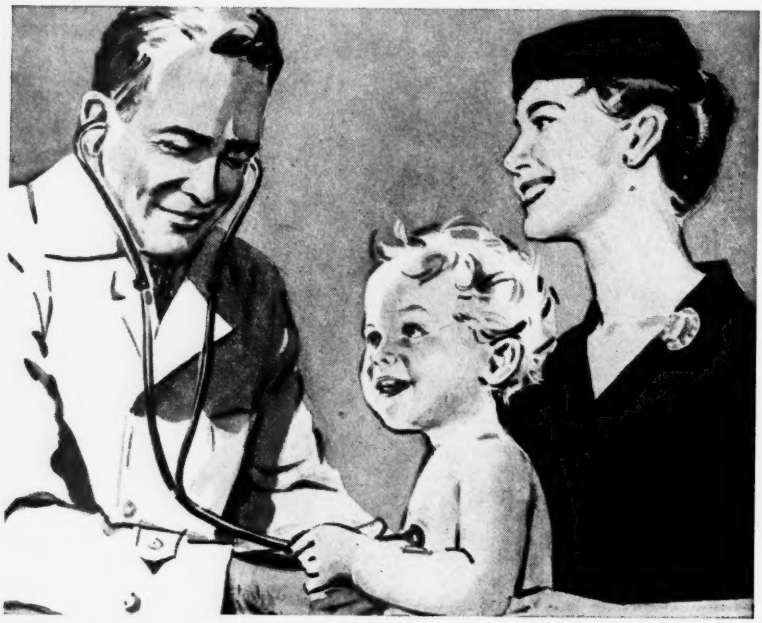
Histology of the tumour showed the characteristic picture of phaeochromocytoma.

After return of the patient to the Paediatric Clinic control showed normalization in all fields, including secretion of noradrenalin, which fell to 12 micrograms per twenty-four hours. It is particularly remarkable that the post-operative regitin test was negative, as shown in Fig. 2, right half.

The electroencephalogram requires a more detailed report. Preoperatively (Fig. 1) it was exceedingly pathological, as mentioned above, and must be looked upon as remarkable. Hypertension with encephalopathy never gives changes of this nature in adults, not even in cases with spasms (Strauss, Mortimer & Greenstein, 1952). In such cases the EEG is normal or shows only minor focal changes. The EEG in question here, however, indicates gross cellular damage as observed e.g. in encephalitis or brain tumour. It must be realized, however, that EEG recordings in severe hypertension in children have been only rarely performed, and it may be imagined that children react differently from adults. As far as the author is aware EEG changes in phaeochromocytoma have not been recorded previously. In the present case the changes have been reversible at any rate, which

Findus producerar — läkaren ordinerar...

Findus barnmat ingår i sjukhusdieten vid många sjukhus och används även som geriatrisk kost.



Det finns tillfällen, då Findus barnmatspuréer på burk kan bli läkaren till god hjälp, t.ex. vid komponerandet av en lämplig diet vid magsjukdomar. Findus barnmat användes redan på detta sätt vid många sjukhus och har även börjat användas som geriatrisk kost.

Vid smärre rubbningar i tarmens funktion — förstoppning eller lös avföring — är ju i lindriga fall katrinplommon respektive blåbär vanliga hjälpmedel av ren huskurskaraktär. Det är därför naturligt att Findus i sitt barnmatssortiment även har en katrinplommonpuré samt en blåbärspuré. Dessa puréer har under flera år utprovats på ett svenskt barnsjukhus, och det är statistiskt fastlagt, att de har åsyftad effekt.

För trög mage – katrinplommonpuré

Lösande verkan vid trög mage har Findus katrinplommonpuré, som är tillverkad av passerade katrinplommon och smaksatt med socker och citronsaft. Näringsvärdet är 182 kcal per burk och smaken sådan att barn med förtjusning äter den t.ex. till gröt eller som efterrätt med mjölk.

För lös mage – blåbärspuré

Findus blåbärspuré verkar stoppande och kan därför med fördel användas vid fall av lös avföring. Purén är tillverkad av passerade blåbär, som sötats med en svag tillsats av sackarin. Konsistensen är halvflytande tack vare tillsats av risstärkelse.

Morotssoppa – recept mot dyspepsier

Att koka morotssoppa på färska morötter är en tidsödande och besvärlig procedur, som kan bereda mamman svårigheter. Överläkare Per Selander, som under många år behandlat svåra dyspepsier med morotssoppa, har därför gjort ingående

försök med soppa, beredd på Findus morotspuré. Dessa försök, som publicerats i Nordisk Medicin nr 29, 1957, visar klart, att denna soppa har exakt samma effekt som en soppa kokt på färska morötter.

Recept

Här meddelas det recept, som användes av dr Selander, och som han ordinerar vid fall av dyspepsier:
3 burkar Findus morotspuré blandas med kokt vatten till 1 liter.
30 gram druvsocker (dextropur).
2.2 gram salt (ungefär 1/2 tesked).
Gives endast på läkares eller barnavårdscentrals ordination.

Dessa fakta är sammanställda av chefen för Findus forskningslaboratorium, docent Carl Erik Danielson.

Tuber om 20, 50 och 100 g

PHARMACIA

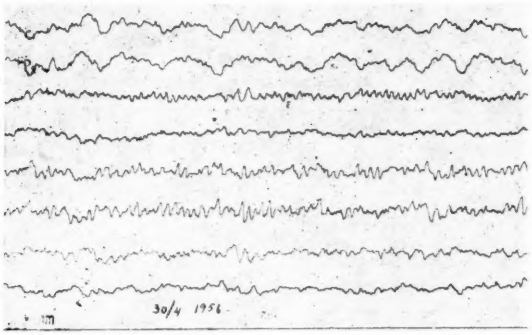


Fig. 3.
EEG after treatment.

appears from Fig. 3, demonstrating the post-operative conditions. The background activity is now normal with a frequency of 7–8 per second, and the potentials are normal. Electrocardiogram, serum chlorides, cholesterol, basal metabolism, ophthalmoscopy, blood sugar tolerance, urea clearance, all showed perfectly normal values. The blood pressure remained —with only small variations—about 100/80. The patient increased in weight, she became psychically normal, and on discharge appeared completely healthy.

Control examination half a year later by the local medical officer showed that she still had a healthy appearance with normal blood pressure.

The clinical manifestations of phaeochromocytoma does not depend only on the quantity of pressor substances emptied into the blood stream by the tumour, but also on the correlation between adrenalin and noradrenalin, as the physiological effect of these substances is not identical. Noradrenalin causes an increase of systolic as well as diastolic pressure, giving marked peripheral vascular symptoms. Adrenalin on the other hand mainly causes only an increase of the systolic pressure.

The rapid and fulminating development of disease in our patient may probably be explained in the first instance by the fact that the tumour was purely noradrenalin-producing. The pain is most likely due to local ischaemia.

In a survey Daechner and coworkers (1954) report that in seventeen children with phaeochromocytoma the symptoms occurred with an incidence as compiled in Table 1.

As will be observed our patient had all the symptoms except retinopathy. Her hypertension was only moderate, but the peripheral vascular phenomena were pronounced. The metabolism could not be determined in the patient, but the polyphagia connected with the loss of weight indicates that it has been increased. Adrenalin and noradrenalin, particularly the

TABLE 1

Symptoms in phaeochromocytoma in childhood.

Symptoms		Number of cases	Our patient
Hypertension	permanent	15	+
	paroxystic	2	
Nervous		16	+
Hyperhidrosis		16	+
Retinopathy		16	0
Tachycardia during rest		15	+
Headache		13	+
Other pain		9	+
Peripheral vascular		12	+
Loss of weight		11	+
Polydipsia		8	+
Polyphagia		6	+
Fasting blood sugar over 80 mg per cent		6	+
Increased basal metabolism		6	+ ?
Constipation		2	+

former, are the only hormones apart from the thyroid hormone, which may increase the basal metabolism.

It may be mentioned as a curious fact that the patient demonstrated a positive Graefe symptom, which persisted during the first few weeks post-operatively. This perhaps confirms the assumption that this symptom, as we know it in Basedow's disease, is a sympathicus phenomenon.

As far as the tumour localization in children below 14 years of age is concerned, a total of 27 cases including the one recorded above, have had the following distribution:

TABLE 2

Localization of the tumour in 27 children below 14 years of age with phaeochromocytoma.

Localization	Number of cases
One suprarenal gland only	18
Both suprarenal glands	3
Extrarenally only	4
Suprarenal glands as well as extrarenally	2

Accordingly this tumour has a far more frequent multiple occurrence in children than in adults, and this probably does a great deal to make the course more fulminating and the prognosis poorer.

Finally, a table is shown indicating the dependence of the prognosis on the treatment, including the present case:

TABLE 3

Prognosis of phaeochromocytoma in children with regard to treatment.

Treatment	No. of cases	No. of fatalities
No operation	4	4
Operation, without use of blood pressure regulating agents	14	8
Operation, with use of blood pressure regulating agents during intervention	3	1
Operation, with use of blood pressure regulating agents during operation and also as premedication	6	0

Summary

A six year old girl in the course of two months developed a dramatically morbid picture with attacks of pain in stomach, throat and back of neck, loss of weight, hyperhidrosis, constipation, polydipsia, and paleness, and also moderately increased blood pressure. After hospitalization convulsive spasms of focal appearance occurred, suspect of intracranial expansive process. Palpation of the abdomen elicited an attack of pain and a blood pressure rise to 210/180. Thereupon constant hypertension of somewhat alternating degree. Greatly exhausted patient with constant attacks of pain and marked peripheral vascular changes.

The regitin test was positive, EEG greatly pathological, and the urinalysis showed very strong secretion of noradrenalin.

The patient received premedication with regitin perorally for five days, the blood pressure thereby falling to 140/100. The condition improved considerably. At operation a tumour of the right suprarenal gland was removed, which demonstrated the characteristic picture of a phaeochromocytoma. She was given noradrenalin intravenously during the intervention, and the following twenty-four hours. The course was uneventful. Complete recovery.

Observation d'un phoéochromocytome chez une fillette de 6 ans.

Apparition progressive, en deux mois, de douleurs dans l'estomac, la gorge et la nuque, amaigrissement, hyperhidrose, constipation, polydipsie, pâleur et hypertension modérée. Spasmes convulsifs d'allure focale faisant soupçonner la présence d'un processus expansif à l'intérieur de la boîte crânienne. La palpation de l'abdomen déclencha l'apparition d'une crise douloureuse et fit monter la tension à 210/180. Cette hypertension se maintint par la suite avec quelques variations. L'épreuve à la Régitine fut

positive; l'électroencéphalogramme était nettement pathologique et l'analyse des urines révéla l'existence d'une forte sécrétion de nor-adrénaline. Un traitement préparatoire comportant l'administration de Régitine par voie orale fut appliqué pendant cinq jours; ce traitement amena l'abaissement de la tension qui s'établit à 140/100. L'état de la malade s'améliora dans des proportions considérables. L'intervention chirurgicale se clôtura par l'ablation d'une tumeur de la capsule surrénale droite qui présentait l'aspect caractéristique d'un phoéochromocytome. La convalescence se déroula sans incidents et aboutit à la guérison complète.

Phaeochromocytom bei einem 6-jährigen Mädchen.

Eine im Laufe von 2 Monaten allmählich fortschreitende Entwicklung von anfallsweisen Magen-, Hals- und Nackenschmerzen, Gewichtsverlust, Hyperhidrose, Verstopfung, Polydipsie und Blässe, wie auch von mässig gesteigertem Blutdruck. Konvulsivspasmus von herdförmigem Charakter mit Verdacht auf einen expansiven intrakraniellen Prozess. Palpation des Abdomens rief einen Schmerzanfall und eine Blutdrucksteigerung bis zu 210/180 hervor. Daraufhin beständige Hypertension von einigermassen wechselndem Grad. Positiver Regitintest, das EEG ausdrücklich pathologisch und starke Noradrenalinausscheidung im Harn. Die Kranke erhielt eine Vorbehandlung mit peroralem Regitin für 5 Tage, wobei der Blutdruck bis zu 140/100 herabfiel. Ihr Zustand verbesserte sich bedeutend. Bei der Operation wurde ein Tumor in der rechten Nebenniere entfernt, der das charakteristische Bild eines Phaeochromocytomes aufwies. Der weitere Verlauf war unkompliziert und führte zu vollständiger Genesung.

Feocromocitoma en una niña de seis años de edad.

Durante el transcurso de 2 meses, desarrollo gradual de ataques dolorificos en el estómago, garganta y dorso del cuello, pérdida de peso, hiperhidrosis, estreñimiento, polidipsia y palidez, así como aumento moderado de la presión sanguínea. Espasmo convulsivo de apariencia focal con sospechas de proceso expansivo intracraneal. La palpación del abdomen elucidó un ataque dolorífico y un alza de la presión sanguínea hasta 210/180. Desde entonces hipertensión constante de grado algún tanto alternativo. La prueba de regitina fué positiva, EEG marcadamente patológica, mostrando el análisis de la orina una muy fuerte secreción de noradrenalina. La paciente recibió una premedicación peroral con regitina durante 5 días, por lo cual descendió la presión sanguínea a 140/100. La condición mejoró considerablemente. Operatoriamente, se practicó la extracción de un tumor de la glándula suprarrenal derecha, por lo que fué demostrado el síndrome característico de un feocromocitoma. El curso ulterior fué sin historia y con curación completa.

References

DAECHNER, C. W., MOYER, J. H. and ABLE, L. W.: Pheochromocytoma in a four-year-old child. *J. Pediat., 45:* 141–152, 1954.

MOORE, TH. and SHUMACKER, H. B. JR.: Adrenalin producing tumors in childhood. *Ann. Surg., 143:* 256–265, 1956.

ROBINSON, M. J. and WILLIAMS, A.: Clinical and pathological details of two cases of pheochromocytoma in childhood. *Arch. Dis. Childhood, 31:* 69–74, 1956.

STRAUSS, MORTIMER and GREENSTEIN: Diagnostic Electroencephalography. Grune and Stratton. New York. 282 pp. 1952.

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The Familial Occurrence of Letterer-Siwe Disease

by W. FALK and B. GELLEI

In recent years workers in the field of Letterer–Siwe disease have centered their interest on the connection between this disease, eosinophilic granuloma and Hand–Schüller–Christian disease. Although it has been mentioned occasionally that the disease can affect more than one member of a family, most writers are of the opinion that Letterer–Siwe disease is neither familial nor hereditary. It may therefore be of interest to report two cases of familial incidence which were recently observed.

Report of Cases

Family 1:

CASE 1.—The patient M. J., 4 years old, was admitted on 9.8.1953 to the Pediatric Department B of the Rambam Government Hospital in Haifa. The child's parents and family, including distant relatives, were all healthy and there was no blood-relationship between the parents, the father being an Ashkenazi Jew and the mother a Sephardic Jewess. When the mother was 19 years old and the father 31 their first child was born a mongoloid. This child died at the age of two years from an unknown cause. Our patient was born two years after the birth of the first child and developed normally both physically and mentally. He suffered of no serious illness. He was sent to our department after having been ill at home for a week with high fever which did not respond to antibiotic treatment. A pediatrician found: enlarged and hard spleen; white blood count 9000 with 36 % neutrophils, 2 % eosinophils, 60 % lymphocytes and 2 % plasma cells. His tentative diagnosis was: diphtheria or infectious mononucleosis and his treatment consisted of 40,000 units diphthera antitoxin.

The patient on admission was well developed and well nourished. His general conditon was relatively good after a week of 40°C. The tonsils were covered with a greyish exudate. The superficial lymph nodes were enlarged, in particular in the left submandibular region. The liver reached one finger breadth below the costal margin and the spleen was palpable on deep inspiration. A number of blood counts during 10 days showed no significant changes from the above-mentioned at the time of admission. Subsequently the white blood count went down first to 4800 and then to 2700. The thrombocyte count went down to 80,000 and then to 22,000. Bleeding time 5 minutes. Blood proteins: 2.8 g % albumin, 2.6 % globulin. Aspiration of lymph nodes produced only blood.

Bone-marrow puncture was performed twice. On the first occasion the result was

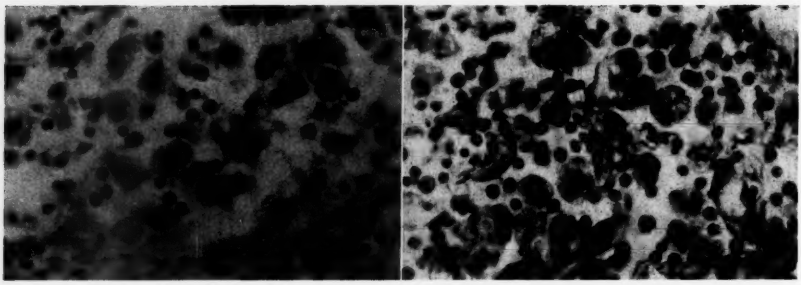


Fig. 1 (*left*). Lymph node (Case 1). Large pale histiocytes in sinusoid. (H.E. × 415.) Fig. 2 (*right*). Thymus (Case 1). Replacement of thymic tissue by large, pale proliferating histiocytes with "foamy" cytoplasma. (Azan × 415.)

(Dr. Salomon): "Active myelo- and erythropoiesis. A few atypical cells were present which might belong to the reticulum cell series." The result of the second examination after 10 days was: "Large elongated cells ... more or less basophil cytoplasma. Some show slight phagocytosis of pigment particles and some seem to store a kind of lipoid substances. The nuclei ... are excentrically located. They show a coarse reticular structure of the chromatin and one nucleolus. These cells are considered to be pathologically changed reticulum cells and their appearance would be in accordance with your diagnosis: acute reticulosis."

Urine examinations revealed traces of albumin and on the last hospital day one per mille albumin, a few leucocytes and hyaline cylinders; urobilinogen + + +. The results of several bacteriological and protozoological stool examinations were normal. Two smears from the tonsils were positive for diphtheria, although virulence-tests were negative. Examinations for Plaut-Vincent and Paul-Bunnel tests were negative. Cold agglutination negative. Serum-diastase 216 Somogyi units. Widal and Brucella agglutination negative. Mantoux 1:1000 negative. Syphilis sero-reaction negative.

Radiological examination did not reveal enlarged mediastinal lymph nodes, nor changes in the bones.

The patient remained in the ward 21 days. During the first and second week his temperature was of the continuous type between 38 and 39°C. During the third week the fever was of the septic type.

Until the end of the third week of the hospital stay there was no change in his condition despite of treatment which included auromycin, penicillin and terramycin one after the other and in the end also cortisone. At the end of the second week in hospital the submandibular swelling greatly increased, as did the spleen and inguinal lymph nodes. A few days later the general condition deteriorated. Melaena appeared and bleeding could not be overcome by blood transfusions. No skin eruption occurred. The child died after three weeks' stay in hospital, i.e. after four weeks' illness.

Necropsy Report. Enlargement of liver, spleen, lymph nodes. Gangrenous pharyngitis and tonsillitis. Scattered ulcerations in colon; massive capillary gastro-intestinal bleeding.

Histological examination. Liver: Large infiltrations of round cells and histiocytes in portal areas. Freely lying histiocytes in central veins. Increased number of large

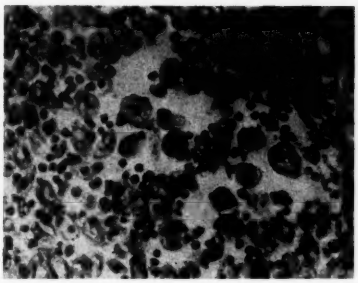


Fig. 3. Thymus (Case 2). Proliferating large, pale histiocytes completely replacing the medullary portion of the gland. (H.E. × 420.)

phagocytes in sinusoids. Areas of central and midzonal necrosis. *Lymph nodes:* Partial loss of structure. Areas of hemorrhagic necrosis. Large number of histiocytes in sinusoids and cords. Phagocytic activity in histiocytes. (Fig. 1.) *Bone marrow:* Many histiocytes mixed with marrow elements. *Thymus:* Complete loss of structure. The whole organ replaced by histiocytes. No Hassal's bodies visible. (Fig. 2.) *Spleen:* Multiple large areas of hemorrhagic infarction. Histiocytes in moderate number still recognizable in sinusoids. *Pancreas:* Interstitial and periductal infiltration by lymphocytes and several histiocytes. *Small intestines:* In Peyer's patches the lymphatic tissue is replaced by reticulum cells. Large necrotic areas with ulceration in mucous coat of colon and inflammation of other layers. *Myocard:* Slight round cell infiltrate interstitial, subepicardially. *Lungs:* Interstitial inflammation; capillary hyperemia. In kidneys, adrenals and brain no pathological findings.

Pathologic-anatomic diagnosis: Reticulo-endotheliosis (Letterer–Siwe disease.)

Case 2.—A few days before M. J. died, his sister A. J., aged ten months, died in another hospital. An autopsy was performed by one of the authors (B. G.) and here also the diagnosis was Letterer–Siwe disease.

Necropsy Report. Marked enlargement of liver, spleen and abdominal lymph nodes. Bilateral hydrothorax; ascites. Massive capillary bleeding from small and large intestine.

Microscopical Report. Spleen: Large hemorrhagic necrotic areas. Elsewhere histiocytes in sinusoids. *Liver:* Large infiltrates in portal areas, smaller around central and hepatic veins. Freely lying histiocytes in central and portal veins. *Lymph nodes:* Large number of histiocytes, foamy, eosinophilic cytoplasma. Phagocytes in sinusoids; also in reticulum mashes of cords. Structure preserved; capsule and surrounding fat and connective tissue infiltrated by large round cells. *Thymus:* Overgrowth of large round histiocytes in cords or lying isolated in medulla (Fig. 3.) *Bone marrow:* High cellularity; scattered histiocytes, isolated or in small groups. *Pancreas:* Interstitial, perivascular and periductal infiltrates, chiefly lymphocytes mixed with histiocytes. *Brain:* Perivascular cuffing of histiocytes in white matter of brain. *Kidneys:* Patchy small cortical infiltrates. *Lungs:* Capillary engorgement. Slight interstitial inflammation. *Heart:* Slight interstitial inflammation.

Family 2:

Case 3.—The patient H. M. E., aged 5 months, was admitted to the Pediatric Department B with the diagnosis malignant tumor with metastases, or systemic

disease of the lymph glands on 12.5.52. His parents who immigrated to Israel from India, are members of a Jewish tribe which has lived in India for many years. The paternal grandfather was the brother of the maternal grandmother. The first daughter was born in India and died there at the age of 6 months. The cause of the death was not established.

Three weeks before H. M. E. was admitted his parents observed a swelling in the inguinal region and after two weeks his temperature rose. He was either crying for many hours, or was sleeping. It was difficult to get anamnestic details from the parents. The physical examination revealed a well-nourished and well-developed infant, weighing 6800 g, not fully conscious; only after gross irritation showed some reaction. In both inguinal regions there were slight packets of lymph nodes, also in the left axillar region. The spleen was palpable 3 cm below the costal arch, and the liver 4 cm, both of them with sharp borders. The temperature was normal on the day of admission, but reached 40.7°C on the following two days. The child had severe diarrhoea, but vomited only once. The white blood count was 4000 with stab 6 %, segmented 26 %, lymphocytes 62 %, monocytes 6 %; hemoglobin 9.5 g %; erythrocytes 3,800,000, very scanty thrombocytes. Erythrocytes sedimentation rate 3 mm/hour. Urine examination: 10–20 leucocytes in a large power field. Bilirubine negative, urobilinogen + + +.

Stool examination: *Proteus morgagni* and *mirabilis*. Mantoux 1 : 1000 negative. Syphilis sero-reactions negative. X-ray examination of the thoracic organs did not reveal pathological changes. A biopsy specimen was taken from the inguinal lymph nodes.

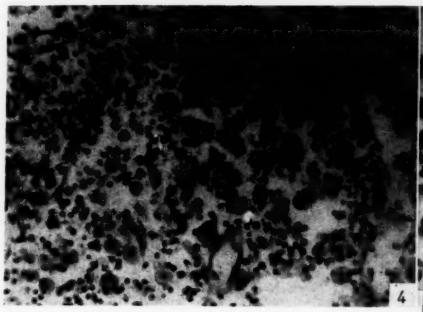
Bone marrow: "Myeloid cells show a relative increase of myelocytes and promyelocytes. Ca. 300 nucleated red cells per 1000 W.B.C., the majority polychromatic normoblasts. Megakaryocytes scanty, no thrombocytogenesis seen. Platelets scanty. There are numerous large cells present with excentric nucleus and a cytoplasma of foam-like structure. These cells are characteristic for lipoidoses of the type Niemann–Pick or Schüller–Christian."

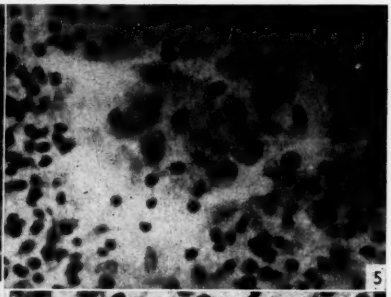
The condition of the child deteriorated very rapidly and he died three days after admission.

Necropsy Report: Enlargement of the liver (285 g); splenomegaly (75 g) with large hemorrhagic infarctions; enlargement of several lymph nodes.

Histological examinations. Lymph nodes: general structure preserved, capsule intact. Follicles small; sinusoids widened and filled with a great number of histiocytes with water-clear cytoplasm. Several of them with phagocyted, nuclear debris. (Figs. 4–5.) *Spleen:* Massive hemorrhagic necrosis. In small rare areas left intact several histiocytes are found in sinusoids. (Fig. 6.) *Liver:* Large infiltrates in portal areas, smaller around central veins, consisting of mononuclear cells. Between them several pale large histiocytes. There are small groups of histiocytes seen freely lying in central veins. In the sinusoids increased number of large phagocytes are present. Scattered through the parenchyma small areas of central and midzonal necrosis are visible. *Bone marrow:* Normal cellularity. Small nests of reticulum cells are present. *Thymus:* Atrophy of cortical layer: large number of reticulum cells infiltrate the parenchyma. Many of the cells have eosinophilic cytoplasma. Hassal's bodies numerous seen. *Kidney:* Focal cortical infiltration of lymphocytes mixed with few histiocytes, near normal glomeruli. *Pancreas:* Heterotopic lymphatic tissue containing large number of histiocytes. *Brain:* Large perivascular infiltrations in subarachnoid spaces in basal region. Perivascular cuffing in basal ganglia. Cells are large mononuclears with several pale, large histiocytes. No lipoids were detectable in the cells.

Myocard, lungs, adrenals, thyroid, hypophysis and intestines without any relevant





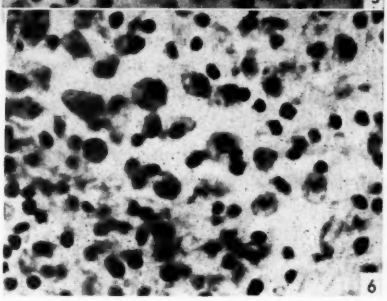


Fig. 4. Lymph node (Case 3). Histiocytes, among them many phagocytes, in cords and sinusoid. (H.E. × 115.)
Fig. 5. Lymph node (Case 3). Nodule of large pale histiocytes in dilated sinusoid (H.E. × 430.)
Fig. 6. Spleen (Case 3). Groups of "foamy" large cells in dilated sinusoid. (H.E. × 430.)

alteration. Contrary to our previous opinion, based on the examination of the bone marrow, the final diagnosis was: Letterer–Siwe disease.

One year after the death of H. M. E. a daughter M. E. was born. She was admitted to the Pediatric Department of Afulah Hospital at the age of 3 months. Examination revealed enlargement of the liver and spleen. "Bone-marrow puncture did not reveal cells of the Niemann–Pick type. Retinoscopy showed a glossy white patch in the form of a disc in the region of the macula and it can be presumed that this is an early form of the macula of Tay–Sachs or Niemann–Pick's disease. The girl was discharged from hospital and the spleen or liver puncture was postponed until a later date." (Translation of the report from Afulah Hospital.)

The child, however, was not returned to hospital, and we were informed that she died a few days later at home at the age of four months. The cause of death was not established.

Case 4.—One year after the birth of M. E., the fourth child was born to Family 2. At the age of 6 weeks he was admitted to the Pediatric Department A of this Hospital. This infant, S. E., was sent to the hospital as the attending physician diagnosed hepato-splenomegaly. Circumcision was performed four days before the child was admitted to hospital, after which it developed fever.

On admission the child was in a good general and nutritional condition. His weight was 4350 g. The only pathological findings were: The spleen was slightly enlarged and the liver reached below the umbilicus. The temperature was between 38 and 40°C. The condition of the child deteriorated rapidly and only a few examinations could be made. Total proteins 5.2 g per cent; albumin 3.9 and globulin 1.3 g per cent. Radiology of the

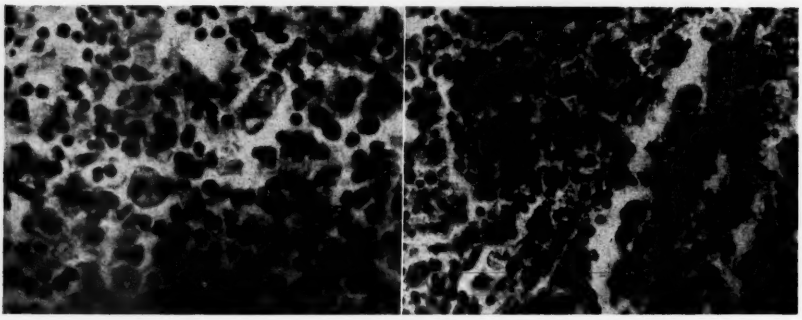


Fig. 7 (*left*). Lymph node (Case 4). Large "foamy" histiocytes in cords. (H.E. × 420.) Fig. 8 (*right*). Spleen (Case 4). Histiocytes in sinusoid. (H.E. × 180.)

skull revealed a rarefied area of the size of a cherry stone which aroused suspicion of eosinophilic granuloma. The infant died after three days in hospital. Letterer–Siwe disease was suspected and this diagnosis was confirmed at autopsy.

Necropsy Report. Hepato- (240 g) splenomegaly (40 g). Enlarged lymph nodes in mediastinum. Bilateral bronchopneumonia.

Histological examinations. Lymph nodes: Partial loss of structure due to necrosis of follicles and cord. Capsules infiltrated by round cells. Large number of mononuclear cells in sinusoids mixed with nuclear debris. Among them histiocytes with foamy and eosinophilic cytoplasm. Several of them are engulfing chromatic particles. (Fig. 7.) *Spleen:* Areas of hemorrhagic necrosis. In sinusoids in preserved portions several pale large histiocytes. (Fig. 8.) *Liver:* Wide mononuclear infiltrates in portal and central areas. Many small necrotic areas in central and midzonal location. Increased cellularity in sinusoids. Among them many phagocytes. *Thymus:* Slight atrophy of organ. Small groups of reticulum cells seen in medulla. *Bone marrow* (ribs): Scattered histiocytes and normal marrow elements. *Lungs:* Hemorrhagic edema in alveoli. Widened alveolar septa due to round cell infiltration. Heart, kidneys, adrenals, brain, cord, intestines and pancreas without pathological changes.

Fifteen months after the birth of the fourth child another daughter, R. E., was born. Birth weight 2920 g; spontaneous delivery at the Rambam Government Hospital in Haifa. The infant's blood was Group B Rh negative while the mother's were 0 Rh positive. No iso-immunization of the mother against the newborn's blood-group antigen B was demonstrated. When 7 months old this child was admitted to our department for follow-up examination. It was a well nourished and well-developed girl in good health. No pathological findings could be detected by physical and routine laboratory examinations. The bone-marrow was normal. Only a few reticulum and plasma cells were present.

Comment

In the case of such a rare disease, it is difficult to imagine that its appearance in siblings is a pure coincidence. This suppositon is even less acceptable

when the disease appears in two families at such a short interval. In the case of this second family it is even reasonable to suppose that three, if not four of the children suffered from Letterer–Siwe disease. In two of them the diagnosis was confirmed histologically by one of us (B. G.). In the case of the girl M. E. the age of the infant, the hepato-splenomegaly and the duration of the illness are all indicative of Letterer-Siwe disease. In consequence it is possible that the first-born infant may also have suffered from the same disease.

The position of Letterer–Siwe disease in relation to eosinophilic granuloma and Hand–Schüller–Christian disease will not be discussed here. There is also a certain relationship—although more distant—to the groups of Niemann–Pick, Tay–Sachs and Gaucher disease which have a definite familial-hereditary character. New vistas were opened up for this group of diseases in a "leading article" in the Lancet (1). In the same issue Grant and Ginsburg (9) state that "the Hand–Schüller–Christian syndrome ... is now recognised as belonging definitely to the xanthomatoses." If it is true to say about the xanthomatoses that "there appears to be no doubt about the origin ... through recessive inheritance" (Gates, 8), then it may be permitted to suspect in regard to Letterer–Siwe disease that a genetic mode of transmission may be possible. Moreover, if the supposed relationship to the leukemias should prove to be true, it is worthy to note that publications have appeared which seem to prove the appearance of this group of diseases in families (2, 3, 10).

Siwe's opinon that the disease is neither hereditary nor familial has become axiomatic. Farquhar & Claireaux (6) go a step further and give a new name to a certain entity, which in our opinion is completely identical with Letterer–Siwe disease, because Letterer–Siwe disease does not appear in siblings. They place doubt on the diagnosis of Reese & Levy (12), who described Letterer–Siwe's disease in siblings, because, they argue, Letterer–Siwe disease in siblings cannot be Letterer–Siwe disease. They claim that the cases which Reese & Levy described as Letterer–Siwe's disease belong to an entity which they have described as "Familial haemophagocytic reticulosis", in spite of the fact that "post-mortem marrow was not typical", i.e. not typical of their new disease, but of Letterer–Siwe disease.

In the family of our first and second patient the child born before these two was a mongoloid. It is to be presumed that this diagnosis was correct and the question arises, if this has any connection with the fact that the two children who were born later suffered from Letterer–Siwe disease. Another point is that in this family there was direct contact between the two children who suffered from Letterer–Siwe disease. In the second family the children were born at such intervals that there could not have been

any contact between them. Thus the belief that perhaps the same noxious agent is to blame here, and that there is no genetic factor, can be dismissed.

The case reports, mentioned above, of Reese & Levy and of Farquhar & Claireaux are not the only ones in the literature concerning the occurrence of Letterer–Siwe disease in siblings. Bierman *et al* (4) in 1952 described two cases of Letterer-Siwe disease in a pair of monozygotic twins and pointed out that up to that time all the 32 cases of Letterer–Siwe disease reported in the literature, since the first description by Siwe in 1924, occurred singly in their respective families. Batson (5) described Letterer–Siwe disease in two siblings who were never in contact with each other. The sibling of another patient died some years earlier from "leukemia associated with a rash". The mother reported that the symptoms were identical. Biopsy or autopsy had not been performed. Freud (7) mentions a personal communication about "three cases of acute, fatal nonlipoid reticuloendotheliosis in siblings of infant age". All these cases would point towards a genetic origin of the disease.

On the basis of our own experience with the two families described, as well as of the cases reported in the literature, it might be possible to conclude that important evidence exists that Letterer–Siwe disease may occur due to a recessive gene in a homozygotic condition. The fact that the parents of the second family were blood-relatives may be another supporting argument—though no evidence—for a recessive gene interpretation. We consider, however, that its familial character is most probably only one of the factors to be taken into consideration. The occurrence of the disease in only one of a pair of monozygotic twins, as has been reported by Lightwood *et al.* (11) may show a genetic character with incomplete penetration and expressiveness. These authors point out the possibility of the existence of the disease in the co-twin in such a mild form that it did not manifest itself clinically.

Siwe's conclusion (13), although not in connection with the familial or genetic character of the disease, can also be associated with our own conclusion, namely: "For the moment we must be content with collecting clinical and anatomo-pathological material which will serve as starting points for further research."

Acknowledgements

We wish to thank Dr. J. Bar-Chaj, Head of the Pediatrics A Department, Rambam Government Hospital, and Dr. E. Nassau, Head of the Pediatric Department, Afulah Hospital, for permission to use the charts of their patients S. E. and M. E.

Summary

Two families are described in one of which Letterer–Siwe disease appeared and was confirmed in two siblings. In the second family the diagnosis was also confirmed by histological examination in two children. Probably in a third child of this family, and possibly in a fourth, Letterer–Siwe disease was the cause of death. The literature about the familial occurrence of Letterer–Siwe disease is reviewed.

Caractère familial de la maladie de Letterer–Siwe.

L'auteur décrit les cas de deux familles. Dans l'une d'entre elles, la maladie de Letterer–Siwe fut diagnostiquée — et ce diagnostic fut confirmé — chez deux enfants. Dans la seconde, le diagnostic fut également confirmé par des examens histologiques chez les deux enfants. Le décès d'un troisième, et peut-être aussi d'un quatrième enfant de cette famille, doivent probablement être également attribués à la maladie de Letterer–Siwe. L'auteur passe ensuite en revue la littérature relative à l'incidence familiale de la maladie.

Familienauftreten der Letterer–Siweschen Krankheit.

Bericht über zwei Familien. Bei der einen trat Letterer–Siwesche Krankheit bei zwei Geschwistern auf und wurde bestätigt. Bei der zweiten wurde die Diagnose auch mit Hilfe von histologischer Untersuchung bei zwei Kindern nachgewiesen. Wahrscheinlich war auch bei einem dritten Kinde in dieser Familie und möglicherweise bei einem vierten Letterer–Siwesche Krankheit die Todesursache. Das Schrifttum über das Auftreten der Krankheit in Familien wird durchgegangen.

Ocurrencia familiar de la enfermedad de Letterer–Siwe.

Relátase el caso de dos familias. En una de ellas la enfermedad de Letterer–Siwe apareció y se confirmó en dos descendientes. En la segunda familia también se confirmó el diagnóstico por el examen histológico de los dos niños. Probablemente en un tercer hijo de esta familia y posiblemente en un cuarto, la enfermedad de Letterer–Siwe fué la causa de muerte. Se revista la literatura existente acerca de la ocurrencia familiar de la enfermedad.

References

1. "Letterer–Christian" Disease. Leading article, *The Lancet, 265:* 541, 1955.
2. Anderson, R. C.: Familial leukemia. *Am. J. Dis. Child., 81:* 313, 1951.
3. Anderson, R. C. and Hermann, H. W.: Leukemia in twin children. *J.A.M.A., 158:* 652, 1955.
4. Bierman, H. R., Lanman, J. T., Dod, K. S., Kelly, K. H., Miller, E. R. and Shimkin, M. B.: The ameliorative effect of antibiotics on nonlipoid reticuloendotheliosis (Letterer–Siwe disease) in identical twins. *J. Pediat., 40:* 269, 1952.
5. Christie, A., Batson, R., Shapiro, J. *et al.*: Acute disseminated (non-lipid) reticuloendotheliosis. *Acta pædiat., 43,* Suppl. *100:* 65, 1954.
6. Farquhar, J. W. and Claireaux, A. E.: Familial haemophagocytic reticulosis. *Arch. Dis. Childhood, 26:* 578, 1951.
7. Freud, P.: Evolution of systemic reticuloendotheliosis in childhood. *J. Pediat., 38:* 744, 1951.
8. Gates, R. R.: *Human Genetics.* Vol. I: 536–537. The MacMillan Co., New York 1948.
9. Grant, L. J. and Ginsburg, J.: Eosinophilic granuloma (honeycomb lung) with diabetes insipidus. *Lancet, 265:* 529, 1955.
10. Guasch, J.: Hérédité des leucémies. *Sang, 25:* 384, 1954.

11. LIGHTWOOD, R. and TIZARD, J. P. M.: Recovery from acute infantile non-lipoid reticuloendotheliosis (Letterer–Siwe disease). *Acta pædiat., 43*, Suppl. *100:* 453, 1954.
12. REESE, A. J. M. and LEVY, E.: Familial incidence of non-lipoid reticulo-endotheliosis (Letterer–Siwe disease). *Arch. Dis. Childhood, 26:* 578, 1951.
13. SIWE, S.: The reticulo-endothelioses in children. *Advances in Pediatrics.* Vol. IV, p. 117. Interscience Publishers, 1949.

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The Appearance of Antistreptolysin and Antistaphylolysin in Human Colostrum

by FOLKE NORDBRING

The transfer of antibodies from the mother to the newborn infant *during gestation* gives the infant protection against a number of diseases, provided that the mother has a sufficient supply of the antibodies in question. This has been shown in numerous investigations.

A comprehensive review of this topic is given by Vahlquist 1952 (52), and the reader is referred to this work. The results of the earlier investigations will be briefly summarized. Diphtheria and tetanus antitoxins, streptococcal erythrogenic antitoxin, antistreptolysin, antistaphylolysin, pertussis agglutinins, typhoid H agglutinins, measles, poliomyelitis, influenza and mumps virus antibodies, toxoplasma antibodies and univalent Rh antibodies are detected in the cord blood in about equal titre as in the blood of the mother. Diphtheria antitoxins, however, often appear in a higher titre in the cord blood than in the maternal (4). Typhoid H agglutinin titres frequently were lower in the cord blood (48, 44).

Some antibodies on the other hand cannot be detected in the cord blood or are found in much lower titre. Among these are coli agglutinins, typhoid O agglutinins, isoagglutinins, bivalent Rh agglutinins and some reagins.

During the last years further studies on prenatal antibody transmission have been carried out. As for diphtheria antitoxin it was shown by Murray *et al.* (28), that *antistaphylolysin* titres in the cord blood usually are higher than in the mother's blood. This was the case in 40 out of 56 pairs of sera. The same phenomenon was observed in the case of *antistreptolysin* (29) in 41 out of 46 pairs of sera. Tunevall (51) demonstrated that the *antipneumolysin* concentration in the cord blood was equal or lower than that in the corresponding maternal blood (70 cases studied).

Cashman (6) confirmed, that *pertussis* agglutinins are present in the cord blood and, again, the cord blood level was above that of the mother in 10 out of 18 instances. Tunevall (50) studied complement-fixing antibodies against *Hemophilus influenzae* in 70 cases. The titres were predominantly considerably lower in the cord blood.

Bacteriostatic activity against *Escherichia coli*, type O 55, was demonstrated by Dancis & Kunz (8) in sera of full-term infants at birth (15 samples) and in two thirds of the sera of premature infants (16 samples). This finding was confirmed by Yeivin *et al.* (58). Neter *et al.* (30) examined agglutinins against *E. coli*, types O 111, 55 and 26, in 26 instances, using the hemagglutination test. They found that these agglutinins were either not transferred to the newborn or were transferred in a low titre. This

observation is in agreement with previous results (3) and it was again confirmed by Yeivin *et al.* (58), who explained the differences in results obtained by Dancis & Kunz and Neter *et al.* on the basis of a difference in sensitivity of the methods employed.

An example of the selectivity in the process of prenatal transfer of antibodies was proposed by Wiener (55), who found that univalent *syphilitic* antibodies, as determined by the Wassermann test, were present in equal amount in the cord and maternal blood in one case. Bivalent antibodies (the flocculation test) appeared in very low titre in the cord blood. These findings have recently been confirmed (54, 10).

Kempe & Benenson (17) determined *vaccinia* antihemagglutinins and complement-fixing antibodies in 182 and 141 pairs of sera, respectively. A large percentage of the cord sera had antibody levels above the maternal sera. Hale & Lee (12) found neutralizing antibodies against *Japanese B virus* in equal titre in 24 pairs of sera. Grasset *et al.* (11), analysing *influenza virus* antihemagglutinins in 201 cases, showed that the infants had the same antibody level as their mothers in 112 instances, the remainder having either lower or higher level.

The last-mentioned workers also found that complement-fixing antibodies against *ricketsia* organisms, causing Q fever, appeared in the blood of the infants of three mothers with a positive titre.

The presence of complement-fixing antibodies and neutralizing antibodies against *toxoplasma* organisms in the cord blood of healthy infants in an amount equal to that of the maternal blood has been confirmed (24, 5).

It is thus evident that the prenatal transmission of antibodies against a great number of pathogens is quite efficient. Already this fact suggests that antibodies appearing in the milk are of minor importance. The presence of antibodies in the blood of the infant at birth of course does not exclude, that a further supply could be received by way of the milk. This might be particularly significant in the case of harmful immune agglutinins due to blood group incompatibility. Also, antibodies which are not transferred during the intrauterine life, especially antibodies against enteric pathogens, might reach the infant by ingestion of *colostrum or milk.*

A review of earlier studies concerning the appearance of antibodies in colostrum and milk is given by Ratner *et al.* 1927 (39, 40). In these earlier works mainly diphtheria antitoxin and coli or typhoid agglutinins were investigated. The antitoxins were found to have much lower titres in the colostrum than in the mother's serum, the agglutinins often were found in higher concentrations in the colostrum.

Further investigations have confirmed the findings concerning *diphtheria* antitoxin. Sugg (47) examined the milk of a woman with an unusually high serum titre. The titre in the colostrum of the first day after delivery was about one third of the serum titre and the antitoxin content then diminished rapidly. A low titre, however, was found in this case throughout lactation. In another study (23), Liebling & Schmitz immunized a group of mothers actively during gestation (17 Schick-negative women). Despite a marked rise in antitoxin in the sera, only a low amount was demonstrated in the colostrum of the third day. The same results have been obtained by others (22, 53).

Lemétayer *et al.* (22) and Debré *et al.* (9) analysed *tetanus* antitoxin. The findings were consistent with those for diphtheria antitoxin: no antibodies could be demon-

strated in the colostrum of the second or third day from six vaccinated mothers (9), low titres were found in the colostrum of the first day (22).

Vignes *et al.* (53) found only very low titres of *antistaphylolysin* in colostrum samples of the second day from 48 mothers. Malmnäs *et al.* (25) reported low antistaphylolysin and *antistreptolysin* titres in colostrum, compared with the titres in the maternal sera. They worked with colostrum samples, collected during the first three post-partum days from about 80 mothers.

An attempt to find out, if agglutinins against *Hemophilus pertussis* are present in colostrum, was made by Adams *et al.* (2). However, a titre was ascertained only in the sera of five mothers and three of these had a low titre in colostrum of the third day.

Several workers have confirmed, that agglutinins against enteric pathogens appear in colostrum in a fairly large amount, often the titres are higher than those in the serum. This was revealed by Timmerman (48) in his study of *typhoid* O and H agglutinins in 32 colostrum samples (first post-partum day). Schubert & Grünberg (44) reported remarkably high typhoid H agglutinin titres in early colostrum samples from 40 women after a single injection of typhoid vaccine during gestation, much higher than in the corresponding sera. Antibodies could be traced in the milk at three weeks after delivery, but no figures were given.

Dysentery agglutinins in milk of a large group of mostly Chinese women were determined by Wong & Wong (57). High titres were obtained in colostrum, secured soon after delivery, in the majority of cases higher than in the serum.

The occurrence of *coli* agglutinins in colostrum has been established by various workers. Toomey (49) examined 25 milk specimens, obtained on the first and the tenth days after parturition. The titres were higher in the early milk but never exceeded the titres in the maternal sera. Schneider & Papp (43) described three cases with a considerable concentration of coli agglutinins in the first day's colostrum, the antibody level being above that in the serum. The same observation was made by Abraham (1) in a few cases. Malmnäs *et al.* (25), in their work mentioned above, also studied coli agglutinins. The colostrum in some cases had a larger content of agglutinins than did the serum, but the highest titre they could ascertain in a few colostrum samples was 1:320, whereas several sera had a titre of 1:640.

Sabin (41) reported the presence in colostrum and milk of a substance, neutralizing Lansing *poliomyelitis virus*. Originally, this factor was not considered to be an antibody, but in a later paper (42) he stated that it probably is. The substance was only demonstrated in milk of mothers with neutralizing antibodies in their sera. The findings of Sabin have been confirmed by Pintér (37), who found neutralizing antibodies in 14 out of 21 colostra with a close correlation to the antibody level in sera.

Rh antibodies and immune *anti-A* and *anti-B* have been demonstrated in colostrum and milk by many authors. These studies have been reviewed by Marrack 1947 (26). Some further contributions in this field have been given during recent years. Speiser *et al.* (46) found Rh antibodies in 23 out of 35 colostrum samples, Kölbl (19) in only 8 out of 34 specimens. Christiaens & Goudemand (7) observed a case of A-B-O isoimmunization. The mother had high serum anti-A titres and extremely high titres in the colostrum. In this case the agglutinins were still present in the milk 17 days after delivery.

That isoagglutinins, corresponding to the blood groups of the mother, appear in the colostrum of the first post-partum days in almost all examined cases, has been shown by Hirszfeld & Lille-Szyszkowicz (14) and recently by Mosler (27).

Finally, *protective factors* have been demonstrated in milk but the nature of these

substances is not well defined. Sabin (41) found that 7 out of 8 specimens of milk had a neutralizing effect on Japanese B virus. There was no parallelism between this effect and the effect on poliomyelitis virus. Kirschner & Maguire (18) detected an anti-leptospiral principle in milk, probably associated with the casein and appearing in higher concentration in matured milk than in colostrum. Inhibition of influenza and mumps virus multiplication (15) and the presence of an influenza virus hemagglutination inhibitor (45) have also been reported.

The investigations cited above indicate that antibodies appear in human colostrum mostly in relatively small concentrations but sometimes, particularly in the case of agglutinins against enteric pathogens and to a certain extent blood group agglutinins, they appear in high concentration. In general, the antibody content decreases within a few days, but some investigators have obtained some types of antibodies in a low titre also in matured milk.

However, mostly the antibody content has been determined in isolated and/or pooled samples of colostrum, and there are few studies on daily samples from one donor. It is the aim of this investigation to follow the antibody titre closely from day to day. In a forthcoming communication the change in protein composition during these days will be reported (31).

In this first paper the occurrence of O antistreptolysin (AS) and α antistaphylolysin (ASta) in colostrum will be reported. These antibodies were chosen, because they are commonly present in the sera of normal persons and occasionally in high titres as a sign of recent streptococcal or staphylococcal infection. It could thus be expected that a sufficient number of women with these antibodies would easily be available.

Material

The material consists of sera and colostrum samples from 108 mothers, admitted to the Maternity Ward, University Hospital, Uppsala. The blood samples were obtained by venous puncture immediately after delivery or on the first or second postpartum day. The blood was allowed to clot and serum was sucked off after centrifugation. The colostrum samples were collected on each of the first five days by manual expression. A few such series were incomplete. Each colostrum sample consisted of small portions, secured as a rule from at least three meals during the day, one part before nursing the baby, one part afterwards. A few samples of the prenatal secretion one or two days before parturition were obtained. All sera and colostrum samples were stored in the frozen state at $-16°$ to $-20°$C until analysed.

Methods

Antistreptolysin

The AS titre was determined according to Ipsen (16) with the modifications proposed by Packalén & Bergqvist (35), using standard antistreptolysin from the State Serum Institute, Copenhagen, and streptolysin from the State Bacteriological Laboratory, Stockholm.

In brief, the procedure was performed as follows. Sera and colostrum samples were inactivated for 30 minutes in a waterbath (+ 56°C). A dilution series with physiologic saline was prepared, beginning at 1:50, in a volume of 0.5 ml. A dilution series of the standard serum was made with diminishing AS concentrations from 1 to 0.2 units. A standard dose of streptolysin was added to each tube in a volume of 1 ml, and after shaking the tubes the lysin was allowed to combine with the antilysin in the sample for 15 minutes in a waterbath (+ 37°C). Before each titration the potency of the streptolysin was assayed and the streptolysin diluted with saline to a standard test dose in a volume of 1 ml. Following the lysin-antilysin combination, 0.5 ml of a 3 per cent suspension of sheep blood corpuscles, washed 3 times with saline, was added to each tube. After shaking the tubes were put into the waterbath (+ 37°C) for 30 minutes. The tubes were kept in the refrigerator overnight and readings were performed next morning.

The hemolysis in each tube was estimated by the naked eye as per cent of total hemolysis. A serum or colostrum dilution which gave 50 per cent hemolysis or an interpolated dilution, giving this degree of hemolysis, was compared with the corresponding effect in the standard dilution series. The titre in the examined sample was then obtained from the schedule in Ipsen's paper (the degree of dilution multiplied by the number of corresponding AS units in the standard series gives the content in the sample assayed).

Antistaphylolysin

The ASta titre was determined according to the method of Packalén-Bergqvist (35), which is directly developed from Ipsen's AS method. Standard antistaphylolysin and staphylolysin were obtained from the State Bacteriological Laboratory, Stockholm. The samples to be tested were inactivated as described. The dilution series started at 1:6.25, in a volume of 0.5 ml. The diminishing ASta concentrations in the standard dilution series were from 0.04 to 0.008 units. The test doses of staphylolysin were titrated to a volume of 0.5 ml, which was added to each tube. After shaking the tubes, the lysin-antilysin combination was performed as for AS. One half ml of a 2 per cent suspension of washed rabbit blood corpuscles was added, the tubes were again shaken and placed in a waterbath as above. After this the tubes were kept in the refrigerator and read the next morning.

As in the case of AS analysis, the dilution of the examined sera or colostrum samples, giving an observed or interpolated 50 per cent hemolysis, was compared with the corresponding dilution in the standard series.

Errors of the methods

The methods employed entail considerable error. For AS determinations the error has been estimated to $\pm$ 20–30 per cent (20, 34). This is mainly due to errors in pipetting, errors in estimating the degree of hemolysis and variations of the red blood corpuscles. Of utmost importance is, that the laboratory assistent has a good experience with the methods.

The analyses were performed in the Bacteriological Laboratory, Uppsala, with the technical aid of skilled assistents. It will be pointed out that the errors of the method have no influence on the conclusions in the present investigation. For this reason no detailed account of the errors will be given in this paper. However, double estimations on a number of samples throughout the investigation have revealed an error in

the case of AS determinations, corresponding approximately to that reported in the literature, and a somewhat larger error in the case of ASta determinations. Marked deviations between two titrations on the same serum were found in a few instances. Similar observations have been made by others (34).

Experimental procedure

The colostrum samples from the first 88 mothers were centrifuged for 30 minutes at 10,000 r.p.m. (Servall Angle Centrifuge, Model SS-2), after which the opalescent fat-free fluid was sucked off for antibody titration. All serum and colostrum samples from each individual woman were analysed at the same time. In some series the colostrum samples were rearranged without the assistent's knowledge of the procedure. A slight subjective influence on the results was occasionally noticed, but this did not alter the results appreciably.

In order to more closely investigate the magnitude of subjective influence on antibody determination, the serum and colostrum samples of the last 20 women were analysed in another manner and served as a "control" group. The colostrum samples were centrifuged for 30 minutes at 2500 r.p.m. (Corda Centrifuge), the bulk of the fat was removed, after which the sample again was centrifuged for 30 minutes at the same speed and the opalescent fluid was sucked off. The material was stored in the frozen state, until all samples in the group were obtained. The samples now were numbered and arranged indiscriminately and analysis was performed in turn.

Determination of AS and ASta in serum-milk mixtures

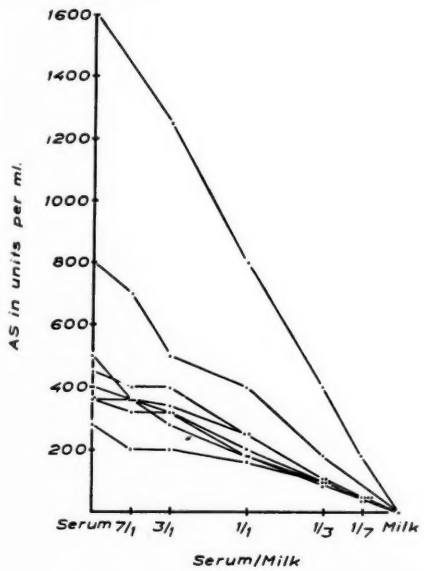
In order to control the reliability of analysis of these antibodies in milk samples and to determine, whether antibodies are lost together with the fat after centrifugation at different speeds, the following procedure was performed. Human milk from breast milk bank, with no antibody titre, was diluted with serum in different proportions, the serum-milk mixture was centrifuged for 30 minutes at 10,000 r.p.m., the fat-free fluid was sucked off and analysed together with the undiluted skimmed milk and the serum, which also was centrifuged. AS was determined in eight such experiments, ASta in four experiments.

The same procedure was again carried out, but the material was centrifuged twice for 30 minutes at 2500 r.p.m. One series of serum-milk mixtures was prepared for each antibody. The sera, the undiluted skimmed milk samples and the fat-free serum-milk mixtures were divided into two parts and scattered among the serum and colostrum samples in the "control" group. Each sample was thus analysed twice independently of each other.

The results of the AS analyses are presented in Figures 1 and 2, the ASta analyses in Figures 3 and 4.

It will be seen, that the decline in titres is approximately linear. The greatest absolute deviations appear when the titres are high, which is expected because of the percental error. No obvious influence due to different centrifugation speeds or different experimental conditions can be detected.

There is thus no evidence, judging from these experiments, of any loss of serum antibodies through the centrifugation procedure, although this might not necessarily be true for naturally occurring milk antibodies. It has been shown, that minute amounts of protein are adsorbed on the fat globules of cow's milk after separation, but chemical analysis of this protein revealed, that it was not identical with lacto-



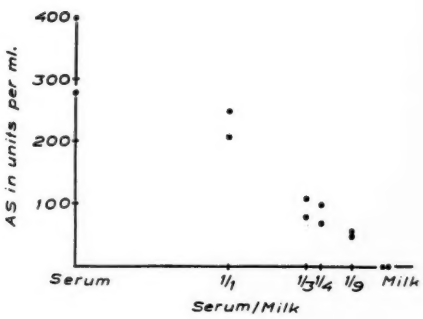
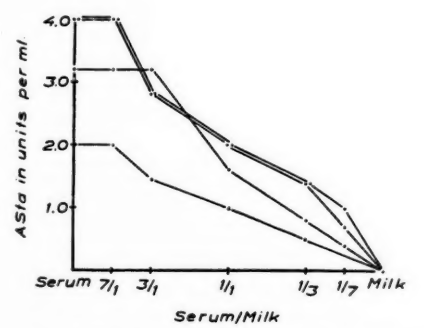


Fig. 1. (*top left*). AS titres in 8 different sera, in matured milk and in serum-milk dilutions in different proportions. Centrifugation was performed for 30 minutes at 10,000 r.p.m. and the fat-free liquid was analysed.

Fig. 2. (*top right*). AS titres in a serum, in matured milk and in serum-milk dilutions. Centrifugation was performed twice for 30 minutes at 2,500 r.p.m. before analysis. Each sample was analysed twice.



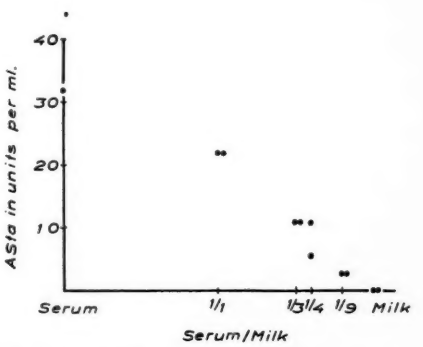


Fig. 3 (*bottom left*). ASta titres in 4 different sera, in matured milk and in serum-milk dilutions. The experimental procedure was identical with that described in the legend for Fig. 1.

Fig. 4 (*bottom right*). ASta titres in a serum, in matured milk and in serum-milk dilutions. The experimental procedure was identical with that described in the legend for Fig. 2.

globulin (36). Presumably the antibodies appear in the "immune globulins". The studies on cow's milk give no indication that this protein is adsorbed on the fat globules.

Results

The distribution of AS and ASta titres in sera and colostrum samples is given in diagrams, Figures 5, 6 and 7.

The titres are divided into six arbitrarily chosen groups. It is readily seen that antibodies appear in highest titre in the colostrum of the first three days. Isolated colostrum samples of the fourth and fifth days have determinable titres, but these are never high. The number of milk samples, revealing an antibody titre, declines steadily from the first to the fifth post-partum day.

This is true for both types of antibodies, which behave almost identically. The pattern within the "control" group of 20 series, represented as black squares in Figures 5 and 6, follows closely that of the first 88 series.

It is also quite evident that the titre distribution in the colostrum samples is entirely different from that in the maternal sera. The titres in the colostrum are as a rule lower. The highest titres, found in sera, do not appear in the colostrum samples.

This is further demonstrated in Figures 8 and 9, which show the correlation between values found in the serum of the mother and her colostrum of the first post-partum day.

It is apparent from the figures that the colostrum titres in general are lower than the serum titres.

In one case the AS titre in the colostrum of the first day was above the titre in the serum (360 and 160 units per ml respectively), in three cases the titres were about equal, but in most instances the AS level was lower in the colostrum. A mother with a high serum titre does not necessarily have a high colostrum titre.

Also in one case the ASta titre was higher in the first day's colostrum than in the serum (1.4 and 0.7 units per ml respectively), in five cases the titres were equal, in most instances the ASta level was lower in the colostrum.

It has been noticed in cases with an antibody titre in the colostrum of the first day that the antibodies either disappeared rapidly or decreased steadily during the next two days or, sometimes, were found in about equal concentration during these days. From the fourth day on an antibody titre could not be determined except in a few cases. This occurred independently of the antibody level in the first day's colostrum.

A few specimens of prenatal secretion were available. The AS values found in these are recorded in Table 1, and for comparison the corresponding

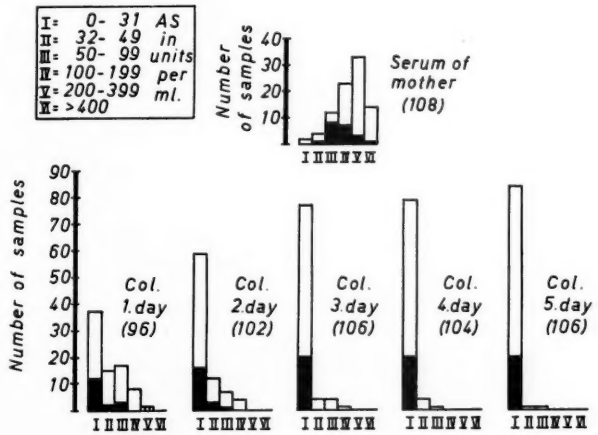


Fig. 5.

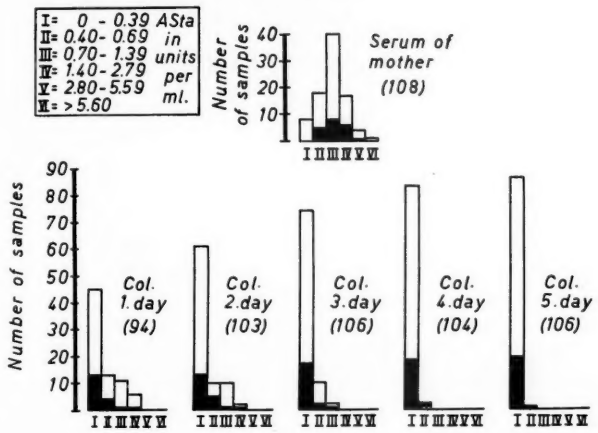


Fig. 6.

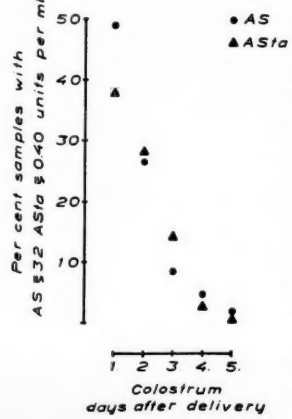
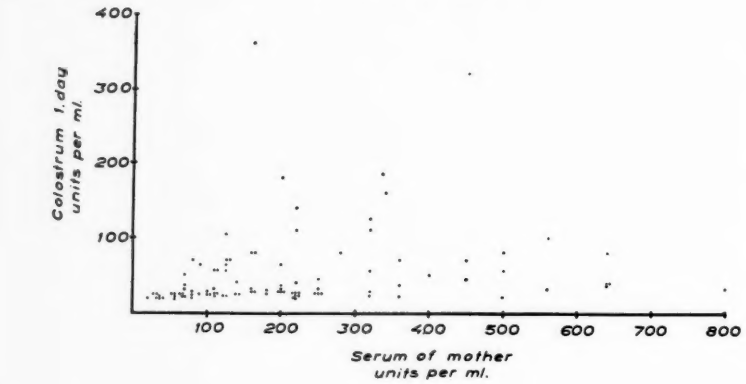


Fig. 7.

Fig. 5. The distribution of AS titres, divided into 6 titre groups, in sera of the mothers and in daily colostrum samples. The white squares represent samples from the first 88 mothers, the black squares, superimposed on the white ones, represent samples from the "control" group of 20 mothers. The lined square (Col. 1. day) means, that the number of samples in this titre group is equal in both groups of mothers. The figures within brackets imply the total number of analysed samples of each type.

Fig. 6. The distribution of ASta titres, divided into 6 titre groups, in sera of the mothers and in daily colostrum samples. The squares and figures within brackets have the same meaning as in Fig. 5, except that the lined square (Col. 4. day) means, that the number of samples in the "control" group of women exceeds that of the other group of women.

Fig. 7. The percental number of different colostrum samples with AS titres above 32 and ASta titres above 0.4 units per ml.



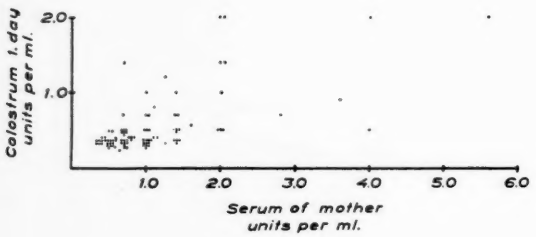


Fig. 8 (*top*). The corresponding AS titres in maternal serum and in colostrum of the first day after delivery.
Fig. 9 (*bottom*). The corresponding ASta titres in maternal serum and in colostrum of the first day after delivery.

TABLE 1

AS titres in units per ml in 8 specimens of colostrum, obtained one or two days before parturition, and titres in corresponding sera and later colostrum samples. 0 = *not determinable titre.*

Case no.	Serum of mother	Colostrum			
		Before part.	1. day p.p.	2. day p.p.	3. day p.p.
23	450	320	320	180	45
24	360	45	22	0	0
33	125	125	125	110	56
54	320	70	56	40	0
84	500	140	80	—	50
86	200	36	0	0	0
90	80	70	70	0	0
97	36	28	0	0	0

TABLE 2

ASta titres in units per ml in 7 specimens of colostrum, obtained one or two days before parturition, and titres in corresponding sera and later colostrum samples. 0 = not determinable titre.

Case no.	Serum of mother	Colostrum			
		Before part.	1. day p.p.	2. day p.p.	3. day p.p.
23	0.5	0.36	—	0.36	0
24	0	0	0	0	0
33	0.4	0.4	0.4	0.28	0
54	1.4	0.5	0.36	0.36	0.36
86	1.0	0.36	0	0	0
90	0.56	0.8	0	0	0
97	2.0	0.4	0	0	0

titres in serum and later colostrum are included. As seen in the table, the titres in these few samples are equal to or higher than the titres in later colostrum samples but mostly lower than serum titres.

The ASta values in prenatal secretion are similarly recorded in Table 2. The same trend is discernible for this antibody.

Discussion

The low concentrations of these antibodies found in colostrum in the majority of cases are in accordance with previous findings (53, 25). Although studies on series of daily colostrum samples as performed in the present investigation are sparse in the literature, there is certain evidence, that the demonstrated rapid decrease in antilysin concentration may be true for other antibodies.

Randall (38) found that the diphtheria antitoxin content in the milk fell rapidly during the first three to four days, but he does not give any figures. Coli agglutinins diminished considerably to low titres on the fourth and fifth days in a small number of examined series (1). A marked reduction in typhoid agglutinin titres from the first to the fifth days was noticed in a study on 13 series (48). Other workers (44) observed a beginning fall in the colostrum typhoid agglutinin titre already on the second day with a steady decline although the presence of agglutinins could be demonstrated as late as three weeks after delivery. Again, no figures are given. Isoagglutinins were reported to disappear as a rule in two or three days, in some cases they were still present in later milk (14). Another study on

isoagglutinins gives clear evidence of a similar trend (27). Rh antibody titres apparently are higher in early colostrum samples than in milk obtained later (19, 46), but small amounts have been demonstrated at one week (56), at two weeks (21) and occasionally in unspecified later milk (19, 46).

The present study and the results obtained by the authors mentioned above suggest that antibodies predominantly appear in the colostral secretion and disappear as the change in character from colostrum to matured milk occurs. Randall (38) states that the decrease is not due solely to dilution but probably also to a decrease in the globulin content. It seems likely, that this statement is true, in regard to the findings by the author in an investigation of the changes in protein composition of colostrum during the first days of lactation (31). It is of interest, that a similar rapid drop in antibody titre, occurring simultaneously with a decrease in "immune globulins", has been demonstrated in a study of paratyphoid agglutinins in the colostrum of vaccinated sows (32). This fall in titre could not be due to dilution, because these animals have a sufficient milk production already at birth.

The cumulative observations of previous investigations together with the results of the present study bring forth some facts, which are of importance in discussing the immunology of the newborn infant. If the mother has antibodies in her blood, the infant will not always be born with these antibodies in his blood. A great number of antibodies, however, appear in the infant's blood in a concentration as high as or even higher than the mother has. Further, if the mother has certain antibodies in her blood, these antibodies will often appear in her milk, sometimes in low concentration, sometimes in high concentration. But the maximal concentration occurs during the first few days, and as a rule there is a steady and often rapid decline in titre during these days.

This means, that the maximal antibody content is found during the period of poor milk production. During this period the baby receives only small quantities of the milk, containing antibodies. Some antibodies have been reported to appear later on, when the milk volume consumed is larger. However, it is apparent from the scanty information available in the literature, that this occurs only occasionally and the antibody titres found are either not stated or found to be low except in a few cases with unusually high concentrations from the beginning of the lactation. Moreover, although unproven, the situation might be that the presumed capacity to absorb antibodies by the newborn infant is greater on the first day or two of life than later on, which has been shown to be true for domestic animals, e.g. calves (13) and piglings (33).

Thus, even if it is presumed that the infant is able to absorb the anti-

bodies, the total amount of antibody ingested as a general rule is fairly small. It therefore appears questionable, that the quantity of antibodies, supplied by way of colostrum, is sufficient enough to increase the titres of already present antibodies, protective against infectious disease or harmful in hemolytic disease, or sufficient enough to give a significant level of antibodies, which are not transferred prenatally.

Summary

Antistreptolysin and antistaphylolysin titres have been determined in sera and daily colostrum samples from 108 women. Forty to fifty per cent of the colostrum specimens of the first post-partum day showed a titre, mostly considerably lower than the corresponding serum titre. There was a marked decrease in antibody concentration during the first three days. Antibodies were traced only occasionally from the fourth day on.

These findings are discussed together with available information in the literature, and it is concluded that antibodies in human colostrum probably play a negligible rôle in development of immunity of the young.

L'apparition d'antistreptolysine et d'antistaphylolysine dans le colostrum humain.

Des dosages de l'antistreptolysine et de l'antistaphylolysine ont été effectués dans le sérum ainsi que dans des échantillons journaliers de colostrum provenant de 108 femmes. Quarante à cinquante pour cent des échantillons de colostrum prélevés le lendemain de l'accouchement présentaient des concentrations nettement inférieures à celles qui furent relevées dans le sérum des mêmes personnes. Une nette diminution du taux d'anticorps a été observée au cours des trois premiers jours. A partir du quatrième jour, les anticorps n'ont été retrouvés qu'occasionnellement. L'auteur commente les résultats de ces observations en les rapprochant des données fournies par la littérature et il conclut que les anticorps présents dans le colostrum ne jouent vraisemblablement qu'un rôle négligeable au point de vue immunologique.

Das Auftreten von Antistreptolysin und Antistaphylolysin im menschlichen Kolostrum.

Antistreptolysin- und Antistaphylolysintiter wurden im Serum und in täglichen Kolostrumproben bei 108 Frauen bestimmt. 40–50 % der Kolostrumproben am ersten Tag nach der Entbindung zeigten einen meistens wesentlich niedrigeren Titer als der entsprechende Serumtiter. Während der ersten drei Tage nahm die Antikörperkonzentration merklich ab. Vom vierten Tag ab konnten Antikörper nur gelegentlich in Spuren nachgewiesen werden. Diese Befunde werden an Hand der verfügbaren Informationen vom Schrifttum erörtert und der Schluss wird gezogen, dass Antikörper im menschlichen Kolostrum wahrscheinlich nur eine unwesentliche Rolle in der Entwicklung der Immunität bei Kindern spielen.

Aparición de antiestreptolisina y antiestafilolisina en el colostro humano.

Han sido determinados títulos de antiestreptolisina y antiestafilolisina en sueros y muestras diarias de colostro provenientes de 108 mujeres. Cuarenta a cincuenta por ciento de los especímenes de colostro del primer día post partum, mostraron un título, por la mayor parte, considerablemente inferior al título sérico que les correspondía.

Hubo nua marcada disminución en la concentración de anticuerpos durante los tres primeros días. Solo se esporearon anticuerpos ocasionalmente a partir del cuarto día. Estos hallazgos están discutidos conjuntamente con la información disponible de provenencia documentaria, y se llega a la conclusión de que los anticuerpos en el colostro humano probablemente desempeñan un papel despreciable en el desarrollo de la inmunidad de la criatura.

References

1. Abraham, G.: Koli und Kolostrum. *Jahrb. Kinderh., 125:* 160, 1929.
2. Adams, J. M., Kimball, A. C. and Adams, F. H.: Early immunization against pertussis. *Am. J. Dis. Child., 74:* 10, 1947.
3. Adamson, C. A., Löfgren, S. and Malmnäs, C.: Antibodies in mothers and newborn infants. *Scandinav. J. Clin. & Lab. Invest., 3:* 52, 1951.
4. Barr, M., Glenny, A. T. and Randall, K. J.: Concentration of diphtheria antitoxin in cord blood and rate of loss in babies. *Lancet, 2:* 324, 1949.
5. Buhn, H. W., Vivell, O. and Richarz, H.: Zur Frage der diaplacentaren Übertragung der Toxoplasmoseantikörper sowie zur Kasuistik der konnatalen Toxoplasmose. *Monatsschr. Kinderh., 100:* 400, 1952.
6. Cashman, A. J.: Early immunization against whooping-cough. Brit. M. J., *2:* 598, 1955.
7. Christiaens, Goudemand: Maladie hémolytique néo-natale due a l'iso-immunisation à l'antigène de groupe A: rôle des agglutinines du lait. *Semaine hôp. Paris, 26:* 3336, 1950.
8. Dancis, J. and Kunz, H. W.: Studies of the immunology of the newborn infant. VI. Bacteriostatic and complement activity of the serum. *Pediatrics, 13:* 339, 1954.
9. Debré, R., Ramon, G., Lévy-Solal, E. and Thiroloix, P. L.: Sur le passage des antitoxines par le lait et le colostrum en particulier dans l'espèce humaine. *Nourrisson, 18:* 235, 1930.
10. Fuhrmann, W.: Über diaplacentäre Übertragung von Lues-Reaginen ohne luische Infektion des Feten. *Monatsschr. Kinderh., 104:* 295, 1956.
11. Grasset, E., de Watteville, H. and Wirth, J.: Passage transplacentaire des anticorps grippaux et antiricketsia et titrage comparatif de ces derniers dans la circulation maternelle et foetale. *Schweiz. Ztschr. allg. Path., 15:* 484, 1952.
12. Hale, J. H. and Lee, L. H.: Transplacental passage of antibody to Japanese B encephalitis virus. *J. Path. & Bact., 68:* 631, 1954.
13. Hansen, R. G. and Phillips, P. H.: Studies on proteins from bovine colostrum. I. Electrophoretic studies on the blood serum proteins of colostrum-free calves and of calves fed colostrum at various ages. *J. Biol. Chem., 171:* 223, 1947.
14. Hirszfeld, L. and Lille-Szyszkowicz, I.: Recherches sur l'immunologie du colostrum. *Rev. immunol., 13:* 265, 1949.
15. Hummeler, K., György, P., Hoover, J. R. E. and Kuhn, R.: Fractions of human milk and virus multiplication. *Science, 118:* 781, 1953.
16. Ipsen, J.: A standard for antistreptolysin O of human serum and its practical application. *Acta path. et microbiol. Scandinav., 21:* 203, 1944.
17. Kempe, C. H. and Benenson, A. S.: Vaccinia. Passive immunity in newborn infants. I. Placental transmission of antibodies. II. Response to vaccinations. *J. Pediat., 42:* 525, 1953.
18. Kirschner, L. and Maguire, T.: Antileptospiral effect of milk. *New Zealand M. J., 54:* 560, 1955.
19. Kölbl, H.: Erfahrungen bei der Behandlung des Morbus haemolyticus neonatorum mit Blutaustauschtransfusionen oder Bluttransfusionen. *Wien. klin. Wchnschr., 63:* 307, 1951.
20. Lagercrantz, R.: Hemolytiska streptokocker och antistreptolysiner hos friska. *Nord. med., 40:* 2143, 1948.
21. Langley, F. A. and Stratton, F.: Haemolytic disease in the newborn. The Rh factor. *Lancet, 1:* 144, 1944.
22. Lemétayer, E., Nicol, L., Grasset, J., Gauthier, R. and Pialoux, J.: Teneur en antitoxine spécifique du colostrum chez les femmes vaccinées par le vaccin mixte antidiphtérique-antitétanique. *Bull. Acad. nat. méd., 134:* 22, 1950.
23. Liebling, J. and Schmitz, H. E.: Colostrum as a source of diphtheria antitoxin in actively immunized pregnant mothers. *J. Pediat., 22:* 189, 1943.
24. Macdonald, A.: Incidence of toxoplasma infection in northwest England. Transmission of antibody from mother to foetus. *Lancet, 2:* 560, 1950.

25. MALMNÄS, C., LÖFGREN, S. and ADAMSON, C. A.: Om övergång av antikroppar från modern till fostret och det nyfödda barnet. *Svenska Läkartidn., 48:* 1737, 1951.
26. MARRACK, J. R.: Antibodies in milk. *Brit. M. Bull., 5:* 187, 1947.
27. MOSLER, W.: Hämagglutinine in der Muttermilch bei homo- und heterospezifischer Schwangerschaft. *Deutsche Gesundheitswesen, 11:* 389, 1956.
28. MURRAY, J., CALMAN, R. M. and LEPINE, A.: Transmission of staphylococcal antitoxin (antihaemolysin) from mother to child. *Lancet, 2:* 14, 1950.
29. MURRAY, J. and CALMAN, R. M.: Immunity of the newborn. A study of the transfer of antistreptolysin from mother to foetus during pregnancy. *Brit. M. J., 1:* 13, 1953.
30. NETER, E., WESTPHAL, O., LÜDERITZ, O., GINO, R. M. and GORZYNSKI, E. A.: Demonstration of antibodies against enteropathogenic Escherichia coli in sera of children of various ages. *Pediatrics, 16:* 801, 1955.
31. NORDBRING, F.: To be published in Acta Soc. Med. Upsala. 1957.
32. —— To be published in Acta Soc. Med. Upsala. 1957.
33. NORDBRING, F. and OLSSON, B.: To be published in Acta Soc. Med. Upsala. 1957.
34. OKER-BLOM, N.: Mean error in antistreptolysin determinations. *Ann. med. exper. et biol. Fenniae, 28:* 107, 1950.
35. PACKALÉN, T. and BERGQVIST, S.: Staphylococci in throat and nose and antistaphylolysin titre. *Acta med. Scandinav., 127:* 291, 1947.
36. PALMER, L. S. and WIESE, H. F.: Substances adsorbed on the fat globules in cream and their relation to churning. II. The isolation and identification of adsorbed substances. *J. Dairy Science, 16:* 41, 1933.
37. PINTÉR, M.: Antibodies to the Lansing strain of poliomyelitis virus in sera and colostra in Hungary. *Acta med. Acad. sc. Hung., 4:* 105, 1953.
38. RANDALL, K. J.: Discussion on immunity responses in the young with special reference to diphtheria. *Proc. Roy. Soc. Med., 42:* 404, 1949.
39. RATNER, B., JACKSON, H. C. and GRUEHL, H. L.: Transmission of protein hypersensitiveness from mother to offspring. II. The rôle of colostrum. *J. Immunol., 14:* 267, 1927.
40. —— Idem III. The rôle of milk. *J. Immunol., 14:* 275, 1927.
41. SABIN, A.: Antipoliomyelitic substance in milk of human beings and certain cows. *Am. J. Dis. Child., 80:* 866, 1950.
42. —— Paralytic consequences of poliomyelitis infection in different parts of the world and in different population groups. *Am. J. Pub. Health, 41:* 1215, 1951.
43. SCHNEIDER, L. and PAPP, G.: Beiträge zur Übertragung der Agglutinine von der Mutter auf das Neugeborene. *Arch. Kinderh., 114:* 91, 1938.
44. SCHUBERT, J. and GRÜNBERG, A.: Zur Frage der Übertragung von Immun-Antikörpern von der Mutter auf das Kind. *Schweiz. med. Wchnschr., 79:* 1007, 1949.
45. SILVER, R., BRAUN, G., ZILLIKEN, F., WERNER, G. and GYÖRGY, P.: Factors in human milk interfering with influenza-virus activities. *Science, 123:* 932, 1956.
46. SPEISER, P., SCHANZER, A. and KARRER, K.: Über Immunkörper gegen erbliche Blutkörperchenantigene in der Muttermilch. *Ztschr. Kinderh., 72:* 509, 1953.
47. SUGG, J. Y.: Diphtheria antitoxin in the milk of a highly immune mother. *Am. J. Hyg., 22:* 227, 1935.
48. TIMMERMAN, W. A.: Zur Frage der Übertragung des Typhus "H"- und "O"-Agglutinin von Mutter auf Kind. *Ztschr. Immunitätsforsch., 70:* 388, 1931.
49. TOOMEY, J. A.: Agglutinins in mother's blood, baby's blood, mother's milk and placental blood. *Am. J. Dis. Child., 47:* 521, 1934.
50. TUNEVALL, G.: Studies on Haemophilus influenzae. A complement fixation test for Haemophilus influenzae antibody. *Acta path. et microbiol. Scandinav., 32:* 258, 1953.
51. —— The antipneumolysin reaction and its clinical application. *Scandinav. J. Clin. & Lab. Invest., 5:* 109, 1953.
52. VAHLQUIST, B.: Placental transfer of antibodies in human beings. *Neo-natal Studies, 1:* 31, 1952.
53. VIGNES. H., RICHOU, R. and RAMON, P.: De la coexistance, dans les sérums humains, des antitoxines diphtérique et staphylococcique naturellement acquises. Leur transmission de la mère au foetus a travers le placenta. Leur élimination par le lait. *Rev. immunol., 12:* 1, 1948.
54. VOGT, E.: Selective filtration of syphilitic reagins through the placenta. *Acta pædiat., 43:* 247, 1954.
55. WIENER, A. S.: The solution of certain fundamental immunological problems by studies on Rh sensitization. *Ann. Allergy, 10:* 535, 1952.
56. WITEBSKY, E., ANDERSON, G. W. and HEIDE, A.: Demonstration of Rh antibody in breast milk. *Proc. Soc. Exper. Biol. & Med., 49:* 179, 1942.

57. WONG, D. H. and WONG, A. I. H.: The significance of dysentery agglutinins in the colostrum and milk. *National M. J. China, 16:* 673, 1930.
58. YEIVIN, R., SALZBERGER, M. and OLITZKI, A. L.: Development of antibodies to enteric pathogens: placental transfer of antibodies and development of immunity in childhood. *Pediatrics, 18:* 19, 1956.

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Active Rickets in a Twin Brother, the Twin Sister Being Healthy

A contribution to the question of a sex-linked aetiological factor in rickets

by GERT v. SYDOW, Sundsvall

On June 21st 1956 I was consulted about a boy, Jan A., born Dec. 27th 1954, because at 1½ years of age he was still unable to walk. His general condition was found to be fairly good, amount of subcutaneous fat, muscular tonus, and colour were satisfactory. Body weight 11,230 g, height 91 cm. Hb 12.4 g %. Micro ESR 14 mm. Nothing abnormal was found in the respiratory system, heart, or abdomen. However, the skeleton revealed pronounced frontal bosses, a slight rosary, extensive enlargements of the epiphyses of the wrists and ankles, and bow legs. Teeth 4/2. The fontanel was open 2 cm. Chvostek sign positive; peroneal sign negative. Serum calcium 7.76 mg %. Serum alkaline phosphatase activity 36 King & Armstrong units. Serum inorganic phosphorus failed by haemolysis.

A roentgenogram of the wrist showed extensive broadening, spurs and fringes of the distal ends of the radius and ulna; pronounced cupping of the ulna; and a streak of increased calcification at the epiphyseal borders of the radius and ulna (Fig. 1).

The history revealed that the boy had a birth weight of 2,730 g and was the first of a set of twins. His twin sister, Karin, born ten minutes later, weighed 2,260 g. They were born at home but immediately afterwards transferred to the County Hospital, Hudiksvall, because the mother had lost a lot of blood and required a transfusion. They were both healthy throughout their stay in the hospital (until Jan. 16th 1955), except that both had a slight thrush infection on discharge. They were both sucking well and no jaundice was ever noticed. Haemoglobin values and erythrocyte counts were, on Dec. 30th, for the boy, 120 per cent and 5.1 mill., and for the girl, 156 per cent and 5.4 mill.; on Jan. 7th, they were for the boy, 95 per cent and 4.9 mill., and for the girl, 152 per cent and 5.3 mill. At home they were both breast-fed for between two and three months and after that given various milk formulas and later a mixed food containing about one litre of milk each daily. During the first winter they were given a vitamin D_2 preparation, dose 2,250 I.U. daily, but not during the summer and not very regularly during the last winter. They have not been taken outdoors very much because they are living in a windy place. Once in the autumn and once in the spring the boy had an upper respiratory infection with fever; the girl, too, had a cold at the same times, but without fever. Apart from this, they had always been healthy. They have been reared together in exactly the same manner. The girl, however, could walk before she was one.

She was also examined: General condition excellent, colour good, ordinary amount of subcutaneous fat, good muscular tonus. She was a little bigger than her twin

Fig. 1. Left wrist of JAN A., the male, rachitic twin, June 21st, 1956.

brother: Body weight 11,920 g. Hb 13.9 g %. Micro ESR 11 mm. Apart from a cervical lymphadenitis the size of a hazel nut nothing abnormal was found in the inner organs. The skeleton appeared entirely normal. Teeth 6/2. The fontanel was open 1 cm. Chvostek sign negative.

A roentgenogram of her wrist showed entirely normal epiphyses. It is remarkable that the osseous centres of her wrist were a little less developed than in her brother (Fig. 2).

The boy was now given a single massive dose of vitamin D_3 (500,000 I.U. by mouth). When he reappeared on July 13th he was able to run fairly well. A roentgenogram of his wrist showed an increased calcification at the epiphyseal border but otherwise pretty well the same findings as on June 21st. The serum calcium had increased to 9.3 mg per cent, and the serum alkaline phosphatase activity decreased to 25 units. He was now given another similar dose of vitamin D_3 and on reappearance on Sept. 6th, he showed a fairly normal skeleton. The roentgenogram showed the epiphyseal borders of the wrist to be no longer broadened, the cupping of the ulna was less pronounced,

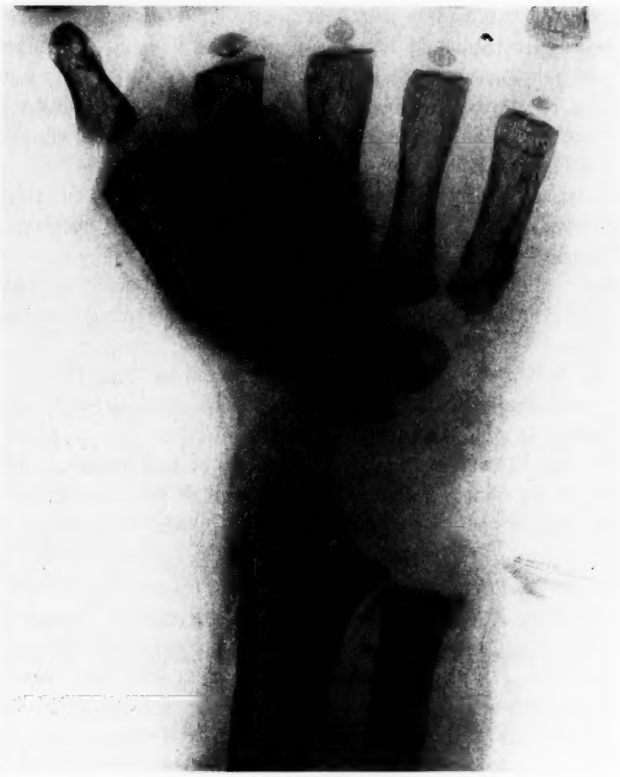

Fig. 2. Left wrist of the healthy female twin, KARIN A., June 21st, 1956.

and there was no fringing or spur formation. There was, however, still a slight irregularity and an increased calcification of the epiphyseal borders.

Thus, the boy acquired a severe rickets while his twin sister has completely escaped it, in spite of the fact that she was considerably smaller at birth and has had identical nursing, food, and vitamin D as her brother. Obviously a shortage in vitamin D or in minerals cannot alone have been the cause of rickets in only one twin. On the other hand, the rachitic process was no doubt of the ordinary vitamin D deficiency type, since it responded very satisfactorily to vitamin D therapy. This case, then, proves that the development of an ordinary vitamin D deficiency rickets may be promoted by some factor which is able to act upon one twin and spare the other. It rests to be established what sort of a factor this may be.

There are only three facts in the history of these children where a real difference can be established between the twins: They are of different sex; the female twin was smaller at birth and has since then grown up somewhat more rapidly than her brother; at birth the boy had a slight anaemia. Further, there is obviously some difference in the hereditary constitution of these two dizygotic twins.

The difference in birth-weight and rate of growth may be ruled out as a cause of rickets in this case, since, according to current opinion, it would rather have contributed to rickets in the other twin.

The same applies to the anaemia found in the newborn male twin, which was mild and can hardly be supposed to be a haemolytic anaemia since both the twins were found to be Rh negative.

The possibility of an hereditary factor in rickets has long been recognized, especially in German literature, though not so often stressed during the recent decades. It was supported to a considerable degree by studies on twins. Lehmann (3) in 1936 reported 124 sets of twins with rickets in one or both twins. In 36 sets the development of rickets was markedly concordant: of these, 28 sets were enzygotic, 8 dizygotic. In 13 sets rickets had developed in only one twin: two of these were enzygotic, 11 dizygotic. From a modern viewpoint the diagnosis of rickets in Lehmann's series is open to criticism since it was established mainly by clinical examination and was often based on the presence of so-called postrachitic deformities. In 1949 Kaplan *et al.* (2) reported a case, very similar to mine, where one twin presented a severe active rickets while the other was found to be entirely healthy. These authors feel that their findings show, in a very impressive manner, the importance of an hereditary factor in the development of rickets.

This may very well be so. There is, however, also another possibility. In Kaplan's case, like in mine, the twin who showed rickets was a boy, the one who escaped, a girl. Out of Lehmann's 13 sets with rickets in only one twin, the twins were of different sex in six and in each of these cases it was the male twin who presented the signs of rickets. This may be connected with some observations on the occurrence of rickets in the two sexes. In a small series I observed, some years ago (5), there was a remarkable difference in this respect. There were twice as many boys as girls in the series, and the rickets was observed at a much earlier age in the boys (before 10 months of age in 31 out of 43 boys, after 10 months of age in 18 of the 21 girls). The same observation concerning the different frequency in the two sexes was made at the same time by Nyrin-Brenel (4) and was verified shortly afterwards in larger series by Flensborg & Thamdrup (1) and by Winberg (6) who could also verify the earlier beginning of rickets in the boys. To these observations of a higher incidence and an earlier occurrence of

rickets in boys may now be added the observations of active rickets in male twins where the twin sisters have escaped. Together, they very strongly support the supposition of a sex-linked factor in the development of rickets, be it that this is an hereditary one or not.

Summary

A case of active vitamin D deficiency rickets is reported in a male twin whose twin sister was entirely healthy. This observation is connected with earlier reports of rickets in only one twin where it was always the male twin who had rickets, and with observations of a higher incidence and an earlier occurrence of rickets in males. Together, these observations very strongly suggest that males are more liable to develop rickets than female infants.

Rachitisme actif chez un jumeau dont la sœur jumelle était en bonne santé.

L'auteur rapporte un cas de rachitisme actif par carence de vitamine D chez un jumeau dont la sœur jumelle était en très bonne santé. Cette observation se rattache à des cas déjà décrits de rachitisme chez un seul jumeau, toujours le garçon, et à des observations selon lesquelles le rachitisme est plus fréquent et se manifeste plus tôt chez les mâles. Toutes ces observations corroborent nettement la supposition qu'un facteur associé au sexe contribue au développement du rachitisme chez les mâles.

Aktive Rachitis in einem männlichen Zwilling mit gesunder Zwillingschwester.

Ein Fall von aktiver, durch D-Vitaminmangel hervorgerufenen Rachitis bei einem männlichen Zwilling, dessen Zwillingschwester vollkommen gesund war, wird beschrieben. Diese Beobachtung wird mit früheren Berichten über Rachitis in nur einem Zwilling, wobei immer nur der männliche Zwilling von der Krankheit befallen war, und mit Beobachtungen einer höheren Inzidenz und früherem Auftreten von Rachitis bei männlichen Kindern, in Zusammenhang gebracht. Alle diese Beobachtungen bekräftigen die Annahme eines geschlechtsgebundenen Faktors, der die Entwicklung von Rachitis bei männlichen Kindern fördere.

Raquitismo activo en un gemelo cuya hermana gemela es sana.

Relátase un caso de raquitismo activo debido a deficiencia de vitamina D en un gemelo varón cuya hermana gemela está en perfecta salud. La observación coincide con reseñas anteriores acerca de raquitismo manifiesto en solo uno de los gemelos, según las cuales siempre ha sido el varón quien estuvo afectado, así como también con observaciones de una más elevada incidencia y aparición más temprana de raquitismo en el sexo masculino. Reunidas, estas observaciones apoyan fuertemente la suposición de que el promotor del raquitismo en los varones corresponde a un factor ligado con el sexo.

References

1. Flensborg, E. W. and Thamdrup, E.: Rachitis og Tetani på börneafdelingerne i Stor-Köbenhavn 1946–1951. *Nord. med., 48:* 1426, 1952.
2. Kaplan, M., Grumbach, R., Cleisz, J.-L. and Cruciani, Ch.: Grand rachitisme chez un frère jumeau, sans atteinte de la sœr jumelle. *Arch. franç. de pédiatrie, 6:* 289, 1949.
3. Lehmann, W.: Die Bedeutung der Erbveranlagung bei der Entstehung der Rachitis. *Ztschr. f. Kinderheilk., 57:* 603, 1936.
4. Nyrin-Brenel, B.: Rachit- och spasmofilifallen vid Göteborgs barnsjukhus 1946–1950. *Svenska läk.tidn., 48:* 3021, 1951.
5. v. Sydow, G.: Analys av fyra års rakitmaterial. *Svenska läk.tidn., 49:* 957, 1952.
6. Winberg, J.: Rachitfrekvensen i Sverige. *Nord. med., 55:* 884, 1955.—The incidence of rickets in Sweden. *Acta pædiat., 44:* 176, 1955.

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PROGRESS IN PAEDIATRICS

Teaching in Social Paediatrics[1]

by ARVID WALLGREN

Introduction

Previously, the practitioner in the Western countries was occupied by caring for people sick with diseases that now, to a great extent have disappeared, for instance, diphtheria, dysentery, infantile cholera, etc. The more these diseases have diminished in frequency, the more time the physician can devote to the promotion of health and the prevention of disease. During his undergraduate studies the medical student should get the education that enables him to procure the type of care that his patients need.

There are three major features of illness: physical, emotional and social. These are so intimately interwoven in the pattern of disease that they must be considered together rather than as separate entities. All three must be included in the curriculum if medical education is to provide the student with the knowledge necessary to fulfil the aims of medicine. One must agree with the Joint Committee of the Association of American Colleges and the American Association of American Social Workers in their report of 1948, that the medical student should learn to recognize and understand the social factors in every case, to evaluate them in relation to the medical problems and to assume responsibility for the relevant problem as a part of diagnosis and treatment.

There is a fund of knowledge relating to the social and environmental factors in pædiatrics that can and should be acquired during the student's education. To teach the student to recognize the importance of social factors in the etiology of the disease is, however, only the first step in this part of his medical education. He must also be taught that it is his responsibility to attend to the mitigation of the influence of adverse social as well as physical factors. To deal with these problems the student must have a basic knowledge of these factors and must develop appropriate attitudes and skills.

[1] Working paper at the WHO Study Group on Pediatric Education, Stockholm 30 July–4 Aug. 1956.

Unfortunately, many students have only slight interest in preventive and social work, which, to the average student, is less exciting than diagnosis and treatment of rare diseases. Neither does the student in many medical schools see very much of the function of the social and health services of the community. After graduation, however, he often has to take over the responsibilities of the running of such a service, without having sufficient knowledge or training to fulfil this job.

The student must understand that he has not only to treat the sick child, but the whole family as a biological and social unit. If one member of that unit is involved in difficulties of any kind, all are involved. This is especially true about sickness in children: he has always to treat at least two members of the family—the sick child and its mother. The family as a unit and the significance of home influences can therefore be particularly well taught in paediatrics.

Terminology

The curriculum of paediatrics includes paediatric education and training in clinical and out-patient departments and education and training in extra-departmental paediatrics. The first term refers to the teaching of the biological development of the child and its needs in various age-groups, of common diseases of childhood, their clinical aspects, prevention and treatment. Extra-departmental paediatrics refers to the environmental conditions and social factors that may influence the life and health of the child and includes public health measures and social services pertaining to children, aiming at their social welfare.

The term "preventive paediatrics" does not cover the whole subject; it is not only a question of preventing illness in children, but of promoting the most perfect physical, emotional and social well-being and adjustment of the child. Neither does the term "social paediatrics" cover the whole subject; social paediatrics is not only the handling of the life of the child in maladjustment to its social environment at home, in the school, in the community, in the group of playmates, in institutions of various kinds, and a knowledge of what is due to maladjustment, but also prevention of these disorders. A combination of the two terms "preventive" and "social" paediatrics, would be preferred, but in order to avoid such a complicated term, some countries use "preventive paediatrics" in the same sense as "social paediatrics". In other countries the term "social paediatrics" is used in the same sense as "preventive paediatrics". In some countries the term "puericulture" is used. The term itself does not matter so very much, if the meaning of the term used is exactly defined and understood.

The Curriculum

There is wide variation as to the amount and quality of the teaching in paediatrics and child health offered in medical schools throughout the world. There is also a great difference in the prevalence of disease and disorders of infancy and childhood and in the nature and load of the responsibilities which practitioners are expected to assume relating to the promotion of health and prevention of disease in infants and children. The education of a medical student in these topics depends also upon his future area of activity, rural or urban, and on the kind of responsibility that he will assume as practitioner or as health administrator. It is therefore difficult to set down any fixed standards for the education of a physician in these topics.

In the economically under-developed countries the prevalence of physical illness in children is so preponderant in relation to other aspects of a child's life that prime attention has to be paid to treatment and prevention of these diseases. The public health aspects will therefore be at the front of the fight for the child's well-being. The more physical illnesses are prevented by unspecific (rised standard of living) and specific (for instance vaccinations) measures, the more emotional troubles and disturbances due to social maladjustment and environmental factors will come to the surface, and their prevention will be one of the most important tasks for the general practitioner. In most European and American countries the public health and social welfare aspects of paediatrics have been emphasized and have become of great importance. The practitioner must know how to handle these problems and the medical curriculum should therefore include corresponding teaching and training of the medical student. The medical shools should be responsible for the student's acquisition of a certain amount of knowledge in this field of paediatrics. The teaching and training of undergraduate students in environmental and social aspects of paediatrics as performed in the paediatric clinics in Sweden will be discussed here.

Demographic Conditions of the Country, Mortality and Natality

The undergraduate medical student should know at least the rough outline of the demographic conditions and problems pertaining to them in his country. He should know the general mortality and natality rate and the general trend of the development of the population and should not be ignorant about the reasons for the present conditions. This is perhaps of special interest in the study of paediatrics, because the developmental trend depends to a large extent upon the annual number of newborn

infants, and the general mortality rate is roughly governed by the death rate of infants.

Concerning natality, the student should be acquainted with the frequency figures from his country in relation to the general trend in other countries and with the consequences of a consistently high (above 20 newborn children per 1000 inhabitants annually) and low (below 20) natality rate for the future development of the population: increase or decrease of the total population. The common causes of a low natality rate, the role of illegal abortions and of voluntary birth control and its causes, the role of the financial situation of the family, of a high standard of living and of the mother's employment, the role of housing difficulties and the lack of help with household work and child-caring, etc., should be stressed as well as the economical consequences to the family of a high natality rate. The students should also know what a "population pyramid" means, with its broad base of infants and its narrow peak of old people, and how such a registration of the population according to age groups may permit a prediction of the future development of the same population.

It is also important to inform the student of the illegitimate birth rate in relation to the legitimate, and to compare it with that in other countries. He should know the many problems an unmarried woman has to face, when she knows she is pregnant, and has to make arrangements for her living during the last months of pregnancy and for her possibility to nurse and take care of the baby herself.

The mortality rate of infants and children and its general pattern is a very important subject and so is the knowledge of prevalent causes of deaths at different age groups. The student should know that newborns and young infants have the highest mortality. He should know the difference between neonatal and late infant mortality rate and the principal causes of death in these two periods of an infant's life: premature births in the neonatal death rate, and infectious diseases in the late infant mortality rate. This knowledge gives him suggestions regarding the manner in which the mortality rate may further be diminished. While the late infant mortality rate has decreased considerably, thanks to measures adopted to improve the feeding and nursing of infants, to prevent infections and to the improvement in diagnosis and treatment of diseases in infancy, the neonatal death rate has remained unchanged. What is known about the prevention of foetal deaths and of premature births should be told to the student, who must also have theoretical teaching and practical training in the treatment of premature infants and knowledge about the saving of their lives.

Another item that should be stressed in this connexion is the cause of death in children above infant age and the changes that have occurred

during the last half century. The student should know that the most important improvement has occurred regarding infectious diseases: diphtheria, dysentery, scarlet fever, tuberculosis and other infections do not at present play any significant role as causes of death in childhood in a well developed country. The more these diseases have disappeared, the more important role do other diseases in such a country play in the general mortality in childhood, for instance, accidents and malignant and chronic diseases. Both traffic accidents and home accidents (e.g. poisonings) have increased, not only relatively but absolutely. This is a big field for research and prevention that should provoke the able family doctor and the medical student to active work.

Legislation Aiming at the Well-being and Treatment of Children

The student must be informed about the legislation and of the legal restrictions and requirements concerning the care and the protection of children in his country. There are in all countries some legal principles aiming at the promotion of the well-being and health of children, of which the student should have at least some knowledge, as it is of importance that he should not overlook their application. The general practitioners, perhaps more than anybody else, get a first-hand impression of the standard of the care of children in the family, and they have a professional responsibility to improve and correct, if anything is wrong. They also have the duty of reporting to the community authorities if the life and the environment of the child is threatening its physical or emotional health. The physician must therefore know what is expected of him in this way and preferably make suggestions himself to the authorities regarding the protection and security of the child in the community.

The student should be informed of the existing laws concerning welfare of children, the legislative rules about the protection of illegitimate children, of the supervision of foster children, of the principles for adoption of children, treatment of delinquent children, etc.

Allowances

Another item of interest in connexion with legislation is the various kinds of allowances that the mother or the family will, more or less automatically, receive in connexion with the birth of a child, or of subsidies to facilitate the economic care of children in the family. The student must know the principles of these allowances and subsidies, the legislation concerning them, as well as their aim and the amount of the allowance. In some countries "child-rich" families are supported economically by reduction of the

taxes, in others by direct allowance, the amount of which depends on the number of children in the family. In some countries there exists so-called "motherhood insurance" by which each mother of a newborn child, independent of the family's economic status, gets an allowance which is supposed to cover the expenses in connexion with the birth of the child and the providing of necessities for the care of the infant and to permit the mother to remain with her child in her own home, or to be admitted to a Mother and Infant Home. In other countries allowances are given only to those who are in need of them.

The student should know what the principles are in his own country, what means and resources there are to facilitate for mother and child to live together during the nursing period, especially how an unmarried mother or a mother with employment may be helped, how a long-term provision of a child may be arranged. He should know what kind of social agencies should be contacted in each case, when the mother herself has to earn her support: day-nurseries, foster parents, adoption, etc.

In many countries there are nation-wide voluntary institutions, funds and agencies that collaborate closely with official agencies, economically and morally supporting the work of the latter. It is of advantage for a practitioner to have information of the existence of such private sources for promoting a healthy life for children and this information should preferably be given during the paediatric course. In addition, the practitioner ought to have information about the existence of all local voluntary funds and agencies in a community where he has started, or intends to start, working as a practitioner.

Environmental Conditions

In order to be able to understand all problems related to the environment in which the child's illness started, and of accommodation possibilities in the home of the child during treatment and convalescence, it is necessary to have an insight into the life of the child in the family and of the family as a unit. One of the very important items is the character of the living quarters of the family, if the family has a house of its own or if they rent an apartment, how many rooms they have at their disposal and how many persons, adults and children, there are in the house. The quality of the housing; ventilation, heating, bathroom and sanitation facilities and water supply.

Also the personal environment is of great importance to know: if the parents live together and if their relationship is satisfactory; the number and age of the siblings and their relationship to one another; if the child is a step-child; if the wife and husband are the parents of all the children

in the family; the occupation of the breadwinner; if the employment has been regular or interrupted by illness, strikes, military service or other causes and, in that case, for how long periods and how often during the last year; the amount of the salary of the father and whether this, together with support from other employable family members, and ordinary subsidies, is sufficient to keep the family, or if the family needs regular relief from voluntary or community sources; the interest of the father in the life of the family members in relation to his own personal interests and hobbies during leisure times (sport, handicraft, reading, alcohol, etc.).

The impression of the mother as the most important person for the child in the family, her competence and interest in rearing the children and running the house in a satisfactory way should be noted. Information as to whether she devotes all her time to household work and to the care of her children, whether she has any leisure hours for herself of whether she is overworked, should be noted. It should also be noticed whether she needs to do vocational work outside the family and why; because she is alone (unmarried, separated or a widow) or because the husband's salary is not sufficient to keep the family, or because she is not altogether satisfied with household work only and wants to have some money of her own; what kind of vocational work is she doing and for how many hours a day? How does she provide for the child or the children while she is not at home: housemaid, grandparents or neighbours, day-nursery or family-day-nursery, etc.? Does she easily stand the double work outside and inside the family, or does it fatigue her in a way that influences the manner in which she does the household work and takes care of the children? Has the close contact between the mother and child been broken temporarily by the mother's illness, or by her absence from home for other reasons? Who has, in that event, taken care of the child in the meantime?

The child's life at home may also be of importance to know. Does he prefer to be alone and occupy himself? Has he siblings as playmates, or neighbours' children? What is the relationship to the siblings? Does the child attend a nursery-school? If a schoolchild, does he like to go to school and how does he progress with school work? Is he interested and successful, or dull and uninterested? What is his relationship to teachers and school mates? Has the child to help the parents at home? Has he any leisure time in the afternoons to himself? Has he permission to invite mates to his home? Does he receive any pocket money and is the amount commensurate with that of his school mates? Does he visit movies, and how frequently? How does he spend the summer holidays: summer camp, farm-house, family's own summer cottage, travelling with the parents, etc.

The influence of certain chronic diseases, their importance and what

they mean to the child and its family, for instance diabetes, epilepsy, asthma, mental deficiency and heart disease, must be discussed with the students in connexion with demonstration of special cases treated in the clinic or at the out-patients department. It should be stressed that everything must be done to promote the acceptance of the disease by the sick child and its parents and that the child should be as little „invalidized" as possible. How to provide the best treatment and facilitate the life of the child with its disease and handicap should be discussed. Such social discussions should be made after a thorough study of the home conditions of the child by the social worker, or by the student himself who may also, at certain times, have opportunity to visit the child's home.

To social paediatrics belongs also the adjustment of the child on admission to hospital or other institution. The student should know the very great variations of the reaction of the child to hospital admission—variations depending upon age, and in children of different populations. The student should also know that depending on the home conditions, a child may sometimes feel greater security and tranquility while in hospital, and there are children who like being taken care of by the mother substitute in the hospital and find the life in the hospital interesting and exciting. He should also know the emotional and physical risks of hospitalization; he should be acquainted with the principles of prevention of emotional disorders and of cross-infections in the hospital, and the importance of regarding the sick hospitalized child as a human being and that sufficient consideration is paid to these experiences and knowledge.

Nutrition

Nutrition is one of the fundamental needs of all living creatures and is of primary importance for the satisfactory development of the child and for promoting its well-being. The provision of adequate nutrition is of great importance as a prophylactic measure and is one of the first-range public health problems. For all ages the food should be adequately composed from a qualitative and quantitative point of view. This is therefore not a specific paediatric problem and teaching about the principles of nutrition has been given before the paediatric studies. In no other age group, however, are the consequences of inadequate nutrition so rapidly developed and so disastrous as in childhood, especially infancy. The knowledge of feeding problems of infants and children is therefore of special importance for education in paediatrics. There are a few characteristic features in infant nutrition that should be especially emphasized in paediatric education: breast feeding, supply of cow's milk, protein and vitamins.

Even if the student has previously been informed in the medical curriculum about the requirements constituting a satisfactory diet, he should receive it anew when he is taught paediatrics because of the intimate relation between nutrition and health at this age, and he gets personal experience from hospitalized or out-patient sick children of what unsatisfactory feeding has meant for the development of the child's illness. He must know the very important principles of breast-feeding, the common problems and difficulties inherent in breast-feeding and how to avoid and treat them. He should have a repetition of what is known to be the food requirements of the lactating mother and be informed of the most common social and economic difficulties many mothers, especially unmarried mothers, meet and have to solve in order to be able to nurse their infants. The student should have heard about breast-milk banks and of their function, and of wet nurses and their problems. He should know the hygiene and sanitary requirements of cows-milk production and distribution, how to prepare formulae for infants and the daily amount of cows' milk they should receive. He should be acquainted with the production of dry milk and concentrated milk and the indications of its use in certain circumstances. The student must know the exact amount of vitamins that the infant and child needs in nutrition, in relation to climate and seasons and he must know how to supply the vitamins.

Another item of importance in nutrition is the indiscriminate use of sweets, candies, chewing gum and similar products. The student ought to be taught the danger for the teeth and for a child's appetite that these sweets may constitute and learn how to diminish their most evident risks as to nutrition and dental prophylaxis in childhood, also information on the artificial fluoridation of drinking water should be given and its consequences stressed.

Genetic and Prenatal Factors Pertaining to the Health of Children

In connexion with clinical conferences on particular cases (Rh-incompatibility, haemophilia, diabetes, allergic disorders, heredo-degenerative diseases, etc.) or in ward-round discussions on such cases the genetic factors of importance for development of disease or influencing the course of disease should be stressed and the student get a rehearsal of and practical application of his previously acquired knowledge of the basic science, human genetics. In the same way the role played by prenatal factors (infections e.g. rubella, syphilis, toxoplasmosis, radiation, the mother's malnutrition or emaciation, narcosis during delivery, etc.) in the etiology of malformations and congenital diseases should be emphasized.

Prevention of Infectious Diseases

General public health aspects on acute and chronic infections prevalent in the country as applied in paediatrics should be taught to the student (methods of detection, disinfection, isolation, notification, etc.) as well as more specific public health measures against some prevalent diseases e.g. tuberculosis, syphilis, rheumatic fever and the use of preventive vaccinations and their evaluation.

Social Aspects of Adolescence

In many medical schools the adolescent age is included in paediatric teaching and in these schools the student should be informed about the changing pattern of some diseases, e.g. diabetes, epilepsy, asthma, at puberty, and of the very important social, emotional and environmental factors influencing development and health in the adolescent age.

Available Social Services

The student should know that there are agencies existing in the community which have to do with the life and health of children in a broader sense, with provision of apartments, relief of the poor, care of alcoholics, responsibility of illegitimate children and control of foster children, adoption of children, correction of delinquent children, etc. These bodies are different in different countries, but they exist in some degree of development everywhere and the student should be taught what agencies there are in his own country. He should be acquainted with the role that various voluntary agencies play in community organizations and affairs. He must learn how to utilize them to achieve the aim of meeting the individual needs.

Special community and voluntary social agencies and services for care and well-being of children should be known. In most communities of developed countries there are three different types of institutions for children. They may be termed open, half-open and closed social service institutions, depending upon the manner in which the child is taken care of in relation to the care of the child in its own home. In the open system the whole responsibility rests with the family and the child lives in its own home, cared for by his parents. To these institutions belong child welfare centres and school health services. In the half-open system the child is taken care of for part of the day by the institution which is responsible for the child during this period of time. The rest of the day and the night the child lives at its own home. Two different types of social services are included in this system: day-nurseries and nursery-schools. In the closed

system the child resides temporarily, or for longer periods, in the institution which has taken over the whole responsibility. Infants and children's homes, convalescent homes and various institutions for children handicapped in different ways, belong to this category.

The student should be acquainted with the function of these different types of institutions and should know the benefits that may accrue to the child and the potential disadvantages. He ought to have visited at least one of each of these institutions during his paediatric studies. At the same time he would receive information about the activity and facts about their importance from a social paediatric point of view.

He should also have some idea about the economic aspects of these institutions and services, the cost of operation and how the economy is guaranteed by support from the State or the community, from private agencies and from parents, etc. It is especially important that he is well acquainted with the activity of a child welfare centre and with school health services, because he himself will probably be engaged in such work after graduation.

Open child welfare services

They are the most important of all social services as they are, or should be, available to all children in the community and are of primary importance in the prevention of disease and promotion of health. Their costs of operation are small in comparison with the cost of other kinds of welfare institutions and their degree of effectiveness. Pre-school children belong to child welfare centres, schoolchildren to the school health service. The manner in which they function is similar and their aim is the same. They may be worked by voluntary agencies, by University paediatric departments or by community social agencies.

Child welfare centres

The student ought to know that the aim of a child welfare centre is to serve as guidance and advice to the mother regarding the feeding and nursing and fostering of her child, from its newborn period until school age, and as control of its development and health. In some centres preventive vaccinations are given in addition. The usual staff of a centre is a physician and a child nurse. The organization of the work may be somewhat different. Genrally it is the nurse that is the most important person of the team, because she does the real field work in instructing the mother during the home visits. Home visiting is an essential feature of a well organized child welfare centre. It gives the nurse the best opportunity to ascertain the conditions of the home, to know the general ability of the mother and to get an im-

pression of the environment in which the infant lives. An able nurse should be received as a friendly guest to the family and as friend to friend she should discuss all the problems of the mother regarding her child.

It should be stressed that the visits of mother and child to the office of the centre are more formal and serve as control of the development of the health of the child by the physician who is able to give advice and answer questions and, at the same time, to get all the information he needs from the nurse about her experience of the child in the meantime between the visits of the mother and child to the office. The visits to the office should, in all events, be limited to those necessary. The distance from the home of the child to the office may also be an obstacle for frequent medical examination. The home visits of the nurse, on the contrary, should be frequent; the younger the child, the more ignorant and less reliable the mother seems to be, the more frequent the visits should be.

The only possible risk a child may run when supervised in this way by a welfare centre is the acquisition of cross-infections in the waiting room of the office. Although the work of the centre is principally only meant for healthy children, it may sometimes happen that the mother, or a child with upper respiratory infection, has broken the rules and is sitting among other healthy children in the waiting room. In under-developed countries where welfare centres are starting, the prevalence of disease is so great and the medical facilities so few, that it would seem impossible to exclude sick children from visiting the office of the centre. On the other hand, respiratory infections are more rare in these countries.

School health services

The student should know the following points about these services. They function in about the same way as welfare centres but, in addition, they must pay attention to the child's fitness for school work in its various aspects. The examinations, including tuberculin testing of children, are usually made routinely at the start of the first school year and then at intervals throughout school life. The home visits of the school nurse may be restricted; her most important work is performed at the office in close collaboration with the school physician. Between office hours the nurse is responsible for the school health work and may herself take care of minor ailments and small accidents happening at school, or refer the children to the school physician or an out-patient department.

The school physician is responsible also for the health of the teachers and other personnel, and for the prevention of infections in the school (for instance, tuberculosis) in teachers or sick children. He should also take into his interest the composition of the school lunch, the hygiene of the class-

rooms and toilets, and the fitness of the playgrounds. The children are referred to him from the nurse, the teachers, or the parents, when the child suffers from some physical handicap or displays some kind of illness, or its behaviour shows some peculiarity, or for any other reason. The school physician takes care of such a child himself or refers him to a specialist or out-patient department. He should examine a child who has been absent from school and decide about the child's fitness for all or part of the school work. In many schools the physician is charged with giving formal sex education, and the nurse is charged with lectures in human biology and health and, in adolescent girls' schools, lectures and demonstrations on the care and feeding of infants. In some schools the school physician gives on demand vocational advice to the parents regarding their children.

The child welfare centre and the school health service are the cheapest of any services for social welfare of children. The children are kept at home at the expense of the family, and the only running expenses of the centre and school health services are the salaries of the physician and nurse, which are very small considering the many children who benefit from the work and the great value of services given in the promotion of health of the child. In selective cases, both these services work in close collaboration with other health and social agencies of the community in order to give the best possible service to the child and for the improvement of the child's standard of living.

Half-open institutions for children

They are of two kinds: whole-day service = day-nurseries and part-day service = nursery-schools (kindergartens). The first-named institution takes care of the child when the mother has vocational work and there is no other person at home to care for the child. The child is brought to the day-nursery early in the morning, when the mother goes to her work, and is fetched by her on her return home from the office or the factory where she is employed.

Day-nursery

It is not of any advantage to the child that the mother leaves him all day long in the care of strangers. The child needs the mother's love and care, which day-nursery children cannot enjoy. There must, therefore, be strict indications for admission of children to this kind of treatment. Usually the reasons are economical: the mother is forced to work outside the home because she is alone or her husband is ill or the salary is not sufficient to cover the expenses of the family. Not infrequently the mother has had vocational training before her marriage, for instance as typist, teacher, physician

or nurse. She loves and is happy with her work, which is a stimulant to her life while her household work is not of sufficient interest to her.

In some cases the mother is physically immature, egocentric, superficial and does not feel any responsibility for her home or her child. Her sole interest is to earn money to buy the things she wants and to provide her with the amount of pleasure and enjoyment that she otherwise should lack. Although her husband's salary may be sufficient to raise the family and although she is not interested in the vocational work, she chooses this means to get extra pocket money.

It is necessary for the medical student to know the background of day-nursery care of children and also to be informed of the disadvantages for the child inherent in this treatment. The disadvantages are the risk of cross-infections; the emotional stress and the lack of tranquillity and security for a sensitive child among the many boisterous children of the day-nursery; the physical stress for infants and small children by being brought even in rain and storm and chilly winter days during the rush hours of the traffic, by bus, tram or otherwise, to and from the institution. The mother, when she arrives home, is tired and her domestic work does not leave her sufficient time to occupy herself with her child as a mother should. Because of fatigue she becomes easily irritated and has no patience with the child. In this way the child has no one to receive his confidence, to take part in his joy and grievances, to answer his questions, etc. These children are frequently unhappy and prone to maladjustment, although superficially they may be trained to politeness and manners in the nursery.

It must be regarded as valuable for all women to get vocational training and education. In many well-developed countries, especially where there is lack of labour personnel, for instance in Sweden, the professional work of women is a necessity. Although day-nursery care for children is a disadvantage for the child, it cannot therefore be condemned but must be accepted as a necessity. A better solution than whole-day institutional care would be part-time work, which leaves sufficient time for the mother to pay due interest to the home and to the care and fostering of her child.

The expenses of running a day-nursery are very high and it would be generally impossible for the parents to pay the total cost, especially if they have several children admitted at the same time. Most expenses are therefore paid from other sources—voluntary agencies, private funds or by subsidies from the community. Those on relief from the community pay nothing at all. Those for whom it may be regarded as a luxury to have a child in a day-nursery, often have to cover all the daily expenses—most parents pay a smaller or greater part of the expenses. The cost per day and per child is often considerably higher than the salary the mother gets from a whole

day's work. The demand for day-nursery placement for children is so great in comparison with the available accommodations that there must be restriction and selection, and only those in real need of the extra income that vocational work can give are accepted.

In the choice of children for acceptance for the day-nursery, age plays an important role. They must have passed the most delicate years of life, during which they have a special need of the mother's love and care in the home; in some countries children are not admitted to a day-nursery if they are below two years of age, which must be regarded as a sound policy. In other countries, even young infants are admitted; as a rule most of the day-nurseries accept children in both age groups.

Family-day-nursery

For some physically and mentally delicate children life in the day-nursery constitutes a special stress and danger. They are almost always acquiring infections and suffer from the noise and rush of the other children in the overcrowded nursery. These children should be kept out of the day-nursery and the mother must care for her child in another way. It would be better for the well-being of the child if it were boarded out in a good foster home.

Many children are better off when they are taken care of in a so-called "family-day-nursery", i.e. a private family with one or two young infants. The mother does only household duties, takes care of her own children, and can also look after one or two more children as paying guests for the day. This system has been practised in some countries, often with great success. From a paediatric point of view, when both the parents and children are healthy, their home clean and hygienic, this is far better than the ordinary day-nursery service for the above-mentioned type of child.

There may be, however, some emotional drawbacks inherent in this system: the child's mother often gets the impression that she loses more of the child's love and affection to the day-nursery foster mother than to the personnel at the day-nursery institution. The sense of competition between the biological and the day-foster-mother will sometimes be felt so strongly that the mother cannot stand the stress and therefore removes her child from the family-day-nursery. Sometimes the family-day-nursery mother falls ill, or for other reasons gives up taking care of the guest child. In this case the child may be moved from one home to another, or to a day-nursery, and thus has no opportunity to feel security and love anywhere.

Nursery-school

The student should be taught that the aim of a nursery-school is quite different from that of the day-nursery. It is an institution where children,

usually aged 3–6, are, for a couple of hours daily, occupied with play and other kinds of enjoyment, together with a restricted number of other children of the same age. It gives the single child opportunity to find playmates, to make friends and to adjust himself to be a member of a group. The children are taught good manners, to be friendly and polite to one another and to adults. The nurse who is in charge of the nursery-school should, of course, have a satisfactory psychological, pedagogical education and training. The student should know that from a medical point of view the nursery-school may be of value in establishing better relations between mother and child. At the same time the few hours in the nursery-school gives the mother time to run errands, pay visits, take a rest or perform household duties, without feeling the responsibility of caring for her child. The risk of cross-infection is minimal because children are not accepted but sent home if they show themselves to be catarrhal, or in any other way ill on arrival at the nursery-school.

The running of the nursery-school per day and child is cheaper than the day-nursery, because there is no need for meals, although meals are desirable, and one nursery-school can accept two sets of children, one in the morning and the other in the afternoon. The nursery-schools are compulsory and free in some countries and run by the State or by the community. Usually the parents have to pay a certain fee towards covering the whole cost per day per child and the rest is paid from private funds or the community.

Before being accepted to a day-nursery or nursery-school, every child should be examined by a physician and a physician should be in charge of the medical supervision of the institution, the localities, the playgrounds, the health of the personnel and the children and a schedule of the occupation of the children.

Closed institution for children

Social services for day and night care of children are of three kinds: institutions for healthy children deprived of their mother's care, institutions for care and treatment of handicapped children and institutions for convalescent care of children.

(1) *Institutions for healthy children.*—The student must know that institutionalization of children for long periods of time does not provide the most satisfactory way of caring for their emotional and mental well-being. Collective care in an infant's home (asylum hospice) can never replace care in a private family. The child seldom finds in an Infants' Home a substitute for the mother, her love and affection and personal interest in the child. The admission of a healthy child to such an institution should therefore

be accepted only when there are no other possibilities of taking care of the child and a stay at an institution should be as restricted and as short as possible. If there is need of a very long "taking-care" of a deprived child, for instance when the parents are dead and there are no relatives who can take over the responsibility, the best solution is to board the child out in a good foster home.

It is not only a disadvantage for the healthy child to keep it institutionalized, but also a very expensive sort of social service. In well-developed countries nowadays there are very strict regulations about admission and care of healthy children to institutions and they are generally accepted only for short periods of time, for instance when the parents are temporarily ill or in order to facilitate the control of the child's health and behaviour before boarding it out as a foster child. Most of these healthy-children institutions belong to the community social welfare service and are run by the community. In some countries, for instance Sweden, private infants' homes are strictly prohibited.

(2) *Mothers' and infants' homes* (*mothers' hospice*).—A special type of infants' homes is that in which the mother with her newborn infant may be admitted immediately after delivery. The student should be acquainted with the following facts. These institutions are valuable in promoting breast-feeding and in helping many mothers to take care of their infants at least during the most delicate periods of their lives. For unmarried mothers especially, admission to such a mothers' and infants' home is often the only solution of her immediate serious problem of how to care for her newborn child. Unmarried mothers seldom have the opportunity to move to their parents' house or back to their own living quarters, which rarely are of such a quality that an infant may be housed there.

The choice of many mothers is to have the infant adopted as soon as possible, or to keep it herself. It is difficult for them to make this decision immediately after delivery and it is necessary to give time to deliberately consider their problem in all its aspects, and admission to a mothers' hospice provides her with such an opportunity. In the meantime, the infant is also provided for in the best way. The mother is taught how to nurse and feed her child, which receives her breast milk at least during the first weeks or months.

The length of the mother's stay is restricted, partly because there must be beds free for new arrivals and partly because it is in the interest of the mother, who cannot usually be absent too long from her work. In the interest of the infant the stay at a mothers' and infants' home should not be shorter than 3 months and not longer than 9–12 months.

As a rule, mothers pay nothing at such an institution, the costs being

covered by the community social service, by private agencies, by insurance or by allowances. The mothers' and infants homes are medically supervised.

(3) *Institutions for handicapped children.*—The student should be informed of the provision made by the community and voluntary bodies for the treatment and care of children with certain types of disorders, such as blindness, deafness, spastics, chronic cardiac disease and epilepsy. He should have a general idea of the scope of these services and their therapeutic possibilities.

Institutions for care and treatment of handicapped children are dependent upon the type of handicap. In all countries there is at least some provision for blind and deaf children and the best developed countries provide institutions for almost every kind of handicap or chronic illness of a child. It is seldom that infants are admitted during the first years of life, when they have special need of love and care from their mother. On the other hand, it may be of importance for the success of treatment of the handicap not to postpone the admission too long. There are usually regulations about the age of admission which, in any event, should not be higher than ordinary school age.

The stay in these special institutions for handicapped children lasts at least as many years as a stay in an ordinary school for a normal child.

Children admitted to an institution for some ailment, for instance deafness, blindness, cerebral palsy, rehabilitation after polio or chronic illnesses, are discharged when they have finished their special school, or they are considered to have acquired sufficient rehabilitation to be able to continue with after-care in their own homes. These children are thus only temporarily, even if for several years, institutionalized. Others must be taken care of for ever and cannot be discharged home, for instance some children with epilepsy or severe mental deficiency, but must at adolescent age be moved from the institution for children to an institution for adults, where they are kept at the expence of the State, community, private bodies or the family.

The children keep contact with their families by visits of the parents to the institutions or of the children to their own homes during the holidays. The equipment and the type of education and training of the staff should correspond to the function of the institution. Big institutions have their own house physician responsible for treatment of the handicapped and for the well-being and health of the children and the health of the personnel. Small institutions provide medical examination and health control by a local general practitioner or paediatrician.

It is helpful to show films of the work of these special institutions, for an example of a disabled and otherwise handicapped child, before and after special treatment and training.

(4) *Convalescent care.*—The student should be reminded that a child treated in a hospital for an illness and considered sufficiently recovered to need no further hospital treatment, is often not fit to start living as before the illness. It is important that during this period of convalescence the child lives in conditions that guarantee wellbeing and continued recovery of health.

A child should not be discharged from the hospital to its family unless one knows that the home environment is satisfactory. An enquiry about this should be made in every case before discharge from hospital. There must be someone at home who is able to take adequate care of the convalescent child. There should not be any acutely ill person in the family threatening the discharged child with infection immediately after returning home. The housing conditions should be satisfactory and the home not overcrowded or noisy. If the conditions are somewhat uncertain the social worker should visit the home before discharge of the child and report her impression. If the child before its illness has had its health supervised by a child welfare centre or by the school health services, these services should be contacted and informed about the illness of the child and of the child's condition on discharge. Home visits by the nurse from the welfare centre or the school nurse may thus provide sufficient control of the child's health during convalescence.

If there is no one at home who can take care of the child during convalescence, when both parents are employed and the child, before its illness, was kept at a day-nursery, or if there is someone acutely ill in the family or the housing conditions are unsatisfactory, with regard to the delicate health of the convalescent child, some other measure must be found for providing adequate convalescent care before discharge. If there is a question of only a few days before the child can get such satisfactory after-care in its own home, the discharge should be postponed, otherwise there may be some relatives or neighbours, well known to the child, that can be of help, or the child sent to a convalescent home. It is the duty of the social worker to help the student to find a solution to this problem which is common in some countries and rare in others.

Summer camps

The student should get some information about the aim of summer camps: providing recreation facilities at a country or seaside resort for a few summer months for urban children, giving them also swimming lessons. Special summer camps for diabetics, asthmatics and otherwise disabled and chronically ill children do exist in some countries. The physician's

responsibility is selection and examination of children, control of the health of the personnel, the water and milk supply, the adequacy and composition of the food, and the hygiene of the camp.

Methods and Techniques of Teaching Social Paediatrics

The content of the desirable knowledge in social paediatrics, as registered above, constitutes a rather extensive range of knowledge, often far too extensive to be covered adequately within the already crowded curriculum of medical schools. Although it is true that some of this basic knowledge may be acquired through personal experience after graduation, much of it cannot be so procured. It requires study and the guidance of capable and experienced teachers to provide the students with the foundation they need in order to understand and evaluate the social and environmental factors in medicine.

The knowledge required for the understanding of these subjects should be brought into the medical curriculum early. The social aspects of medicine clearly constitute as much of basic science as physiology or anatomy, and should be taught during the pre-clinical periods. Application of this knowledge should be referred to the clinical years, when the student can use it in dealing directly with patients. The student must learn to recognize and evaluate social and environmental factors in every case. He must develop certain attitudes which will help him to develop effective and wholesome relationships with the patient and with his family, as well as with his colleagues. Because the visits of the parents to the wards are often restricted the student has infrequent contacts with mothers of the sick hospitalized children, but this will be improved when the system of permitting more or less free visits to children's hospitals is more commonly introduced. In all events, the students have an opportunity to contact the parents at the out-patients department.

A few schools have offered a series of lectures that deal exclusively with the social and environmental aspects of paediatrics. In many teaching hospitals it is customary to include in the records a summary of important findings of the social workers and their action on the case.

Preventive and curative paediatrics should be brought into close relationship. In practice it is impossible to make a clear distinction between preventive and curative services. There is an increased recognition of the interdependence of health and social factors, of the value of the family approach and of the closest possible integration of preventive and curative health services.

The professors of paediatrics in my country therefore recommend and

prefer teaching social paediatrics on ward rounds or at clinical conferences, where it can be brought into the discussion on the patient and his problems as seen in their natural relationship to the other aspects of his illness. The student then has the opportunity of applying the knowledge he has gained during his pre-clinical studies. Some professors are of the opinion that teaching in social paediatrics requires no special courses but can be adequately covered in the routine handling of patients on the wards and at the out-patient departments.

The choice of topics in social paediatrics and the relative amount of time devoted to each, will depend upon the previous training and experience of the student, upon the information readily available from other sources, the relative value of the subject under consideration and the importance of the information as it relates to prevention of disease and to the well-being of the child. The teaching should be done by instructors, who are not only thoroughly familiar with and enthusiastic about their subject, but who also have acquired the techniques of teaching and conscientiously apply them in their education of the students.

The weak point in hospital undergraduate training in preparation for practice lies in the difficulty in providing suitable practical experience in social paediatrics. The establishment of training areas in relation to the medical school would provide practical experience in social activity and administration to undergraduate students. Field visits may be made by small groups of students to health departments, to various social services for children in the community, and to social agencies in the community. The best results are obtained when there is some form of orientation as to what facilities are available, with conferences both before and after the trip to clarify the functions of these agencies and services. It is essential that the aim and function of these services and agencies have been understood by the students and that they know in advance what particular things to look for.

Social workers should be used to assist in teaching social paediatrics, because they have special knowledge and training in the social aspects of paediatrics, and because they can inform and show the students how to use the available social services in particular cases. Conferences and consultations between student and social worker concerning the patients are most valuable. The potential contributions of the social worker in social paediatric teaching has not everywhere been utilized to the extent that might be expected. As a rule the social worker is present at the ward rounds. Weekly medical, social and psychiatric ward rounds are held in our clinic during which the social worker and a child psychiatrist attend and freely discuss the problems that a sick child may raise. The social worker plays

an important role as a consultant in social problems and her position in the clinical team is justified.

The guidance of individual students is perhaps the most important contribution of the social worker to medical teaching. By frequent informal discussions with the student, the social worker is able to help him with his case-study, to provide him with data concerning social resources and act as contact between the student and the social agencies he may have to call upon.

Post-graduate Training in Social Paediatrics for Paediatricians

The post-graduate specialist training should include all the items mentioned in the undergraduate curriculum but provide in addition more detailed knowledge and extensive personal experience in the different fields of social services. The resident should act as deputy physician in child welfare centres, school health services, at half-open and closed institutions for children in order to get the necessary personal experiences.

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Section of Pediatrics and School of Hygiene of the Swedish Medical Society

Meeting March 8, 1957

L. Ström: **Oral BCG vaccination.**

A brief review is presented of the oral BCG vaccination. The oral method is especially employed in Brazil and other South American states. It is emphasized that very little basic research or experimental work are available to substantiate the immunity, or degree of immunity, that is produced by this form of vaccination. In order to elucidate this question a series of experiments on animals was conducted in Stockholm in cooperation with Dr. J. Sternberg of Montreal. We made use of BCG tagged with radioactive phosphorus and guinea pigs served as experimental animals. The tagging technique of BCG I have accounted for earlier. The tagging was done by Sievers in Gothenburg and the vaccine, besides being tagged, was a normal vaccine. The speed with which the radioactive material appears in the blood is less by oral vaccination than by parenteral vaccination, even if the oral dosage is ten times greater than the parenteral dosage. The oral absorption of tagged BCG is not influenced by previous immunization of the animal, but as soon as absorption has taken place, the radioactivity is distributed in the immunized animals in a different manner from that in the non-immunized animals. In previously immunized animals the radioactivity is excreted with the urine almost as rapidly whether the tagged BCG is administered intracutaneously or orally. If on the other hand the tagged vaccine is deposited directly in the stomach through a catheter, the radioactivity is excreted with the urine at a considerably slower rate and only slightly faster than in the non-immunized animals. In cases in which the tagged vaccine is held for some time in the mouth, the vaccine is resorbed approximately 4 times as readily as through the gastric mucosa. In cases in which the tagged vaccine is placed directly in the stomach through a tube, three-fourths of the vaccine passes through and is excreted without resorption.

Discussion.—*A. Wallgren:* De Assis calls his oral vaccination "concurrent" because he considers that, when he vaccinates in tuberculous families, BCG then competes with the virulent tubercle bacilli. By means of repeated oral vaccinations, de Assis, in opposition to everybody else, proposes to develop an insensitivity towards tuberculin. The excessively optimistic reports from Brazil have unfortunately not been confirmed to date by others. If this vaccination method should fulfil the promises advanced by Brazilians, then it would naturally become "the method of choice" inasmuch as it would no longer be necessary to ascertain whether the vaccinated person is already infected with tuberculosis. Ström is the first who by direct study has attempted to clarify this problem, and it would be of considerable value if we were to obtain further equally reliable and scientific studies which might shed more light on the theoretical assumptions and practical applications of this method of vaccination.

R. Lagercrantz, E. B. Nordlund, J. Winberg and R. Zetterström: **Systematic manifestations of ulcerative colitis.**

An account is given of a material comprising 47 cases of ulcerative colitis of which 18 showed manifestations in organs other than the colon. Changes of various sorts in the skin were most commonly observed, including one case with butterfly-patterned exanthema and skin necroses in 4 cases. Cultures made of 2 of the latter gave negative results. There was P.A.D. in 3 cases, 2 of which presented vascular changes, and follicular hyperkeratosis of the type observed in erythematosis in 1 case. Cortisone treatment in 3 cases produced healing of the necroses. Erythrocyturia of highly variable degree in 6 cases, as a rule without albuminuria and no signs of renal insufficiency. Definite inflammation of the liver in 3 cases and stasis icterus in all of them. Laparatomy in 1 of these revealed liver studded with miliary necroses, significant enlargment of hilum glands producing compression of choledochus. General hæmorrhagic diathesis in 3 cases, one of which seemed vascularly conditioned, and another apparently depending on the appearance of a thromboplastinin inhibitor. In 1 case disposition for appearance of local oedema, including the larynx, giving rise to such severe obstruction that tracheotomy was required. Arthralgia, myalgia and stomatitis in several cases. Significant increment in gamma globulin in 34 out of 38 cases. The role played by the allergic reaction in giving rise to such diversified manifestations in sundry organs is discussed. Changes in the internal organs may be interpreted as tissue injuries provoked by substances resorbed from the colon and having antigenic properties. This supposition is supported by the fact that ulcerative colitis practically invariably presents manifestations in various internal organs, and also that following colectomy these manifestations disappear in many cases. The increased gamma globulin production may be due to antibodies produced against the above mentioned hypothetical antigen.

C. G. Bergstrand and C. A. Genzell: **Pregnandiol excretion in children.**

Excretion of pregnandiol with the urine was determined in 85 children, 3 to 15 years of age, by a method originated by Klopper and co-workers. Forty-eight girls and 39 boys without metabolic or endocrine disturbances were examined. The boys excreted an average of 0.75 mg pregnandiol per 24 hours and the corresponding figure was 0.72 mg for the girls. These values nearly correspond with the findings in normal men and in women during menopause. Three girls with regular menstruations showed markedly high values during the premenstrual phase. No correlation could be established between pregnandiol excretion and the age of the children. Fourteen children affected by different endocrine disturbances showed normal values of pregnandiol excretion. Six children with congenital adreno-cortical hyperplasia were examined. Before treatment with cortisone these children presented very high values of pregnandiol excretion. During treatment with adreno-cortical steroids a marked fall in pregnandiol excretion was noted.

R. Lagercrantz: **Iron poisoning.**

The poisonousness of ordinary iron preparations does not appear to be recognized by the public nor to be appreciated by physicians in general. The pathogenesis, symptomatology and treatment of iron poisoning will be illustrated on the basis of 3 cases. Vomiting, cold sweating and pallor appeared within an hour after eating the tablets.

An hour or two later the child had diarrhoea, became somnolent or unconscious and on being admitted to the hospital was in deep shock, with cyanosis, tachycardia and low blood pressure. An 18-month-old boy, who had eaten at least 10 tablets of Ferrofer Fort. (containing about 5 g iron sulfate) died 4 hours later. Necropsy revealed blood-congested internal organs, petechiae and oedema in the brain but without any necrosis in the stomach, liver or the intestines. A 20-month-old girl, who had eaten about 20 tablets of Ferrofer Fort. with laxative (the latter played no apparent role), survived following an exchange transfusion. The iron in the serum was estimated to be 434 gamma per cent before the exchange transfusion, 204 gamma per cent immediately afterwards and 45 gamma per cent 2 days later. A 2-year-old who had eaten at least 50 tablets of Kalcifer (containing about 6 g iron tartrate), survived after intensive treatment with intravenous drip and stimulation as well as antidotes in the stomach. Previously it was considered that the symptoms of iron poisoning were produced by the necrosis in the gastro-intestinal mucosa. It is now known that large amounts of iron are resorbed through an intact mucosa. The binding capacity of the iron-bearing albumin is exceeded and the excess iron exerts a toxic effect on the cells. It adheres to the SH-group and inhibits cell respiration and thus inactivates the noradrenalin. The shock, cerebral intoxication and subsequent liver damage play a central role in the pathogenesis. Differences in the poisonousness of various iron preparations would seem to depend on their resorption capacities. Treatment must purposely aim at the prevention of further iron resorption. Gastric lavage may prove dangerous and should always be carefully conducted. Sodium-bicarbonate, bismuth-subcarbonate, beaten egg-whites and milk should be administered in order to bind the iron and prevent necrosis of the mucosa. Shock should promptly be treated with heat applications, intravenously injected fluids (blood, glucose) and noradrenalin. Exchange transfusion would seem indicated. Administration of EDTA and iron-free transferrin is recommended. In order to prevent injury to the liver, large doses of tocopherol, methionin and vitamins should be given. Most important is prophylaxis. It would seem inadequate only to inform the public and physicians about the poisonousness of iron preparations. One should also prevail upon the pharmaceutical industrialists to place iron preparations into bottles or tins supplied with the screw-cover described by Dr. Christiansson. This cannot be opened by youngsters under 5 years of age and should also serve as a constant reminder of the poisonousness of the enclosed preparation.

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BOOK REVIEWS

Stind Sandels: **Utvecklingspsykologiska beteendestudier (Developmental Psychological Behaviour Studies).**

Uppsala, 1956, Kr. 25. —/

The authoress, who by means of this investigation has become Sweden's first kindergarten-teacher to earn her doctor's degree, in this work makes an attempt to compensate for what has hitherto been a lack in child psychology research, partly in regard to infants up to school age and partly in developmental analyses conducted on a broad basis.

This work comprises 460 children aged 1.5 to 8.5 years, all of whom were confronted by similar tasks of three types: assortment (for example of dissimilarly coloured pearls from a box), division (of a plasticine cake into a variable number of dolls), and assembling (of balls into a basket). Each of the experimental situations thus had an indefinite character and offered opportunities for wide variations in behaviour, which could all the same be subjected to analysis and the results submitted to statistical evaluation. The study offered possibilities to discern development not only in these functional tasks, but also in general behaviour, and moreover showed good agreement with the findings by Gesell and Piaget. The principal discovery is that developmental processes in these age groups are organized under quite a complicated interplay of an infinitesimal number of functions, psychological as well as physiological. Every subdivision into levels and stages and more localization of these into certain age groups becomes therefore purely arbitrary. Certain maturity levels can be separated, but the dynamics within and between dissimilar stages are always lively.

This study also offers a sound basis for further investigation in clinical child psychology, especially with reference to the ability to make diagnosis on the basis of dissimilar assortment tests, as has been done by investigators like Goldstein, Strauss, Werner and others. It is regrettable that this study is written in Swedish even if it does contain quite an extensive general review in English.

Lars Billing

André Thomas, Yves Chesni et M^{me} St-Anne Dargassies: **Examen Neurologique du Nourrison.**

Edité par La Vie Médicale, Paris, 1956, 47 pages, richly illustrated.

This booklet is written by the child-neurologist team working in Paris under the direction of André Thomas, which has previously published a great number of works dealing with the neurology of the newborn and of infants. The actual work is divided into two sections. The first deals with the newborn age-period. The authors offer detailed guidance on recording the newborn's anamnesis and of examining cases suspected of having sustained injuries to the central nervous system. A refined physical examination procedure is described in detail and is illustrated with exceptionally good pictures. The second section deals with the infant up to one year of age. Here an

account is given of the normal infant's development and growth. The reactions and reflexes which were described in the first section are discussed in relation to their development and disappearance as well as transitions into reactions of the adult type. By means of directions for carrying out a detailed examination of the child's motorial development, tonus, reflex activity, etc., one is able to estimate injuries to the child's central nervous system and to diagnose and commence treatment at an early stage whenever it is indicated. The publication is recommended to paediatricians who specialize in diseases affecting the child's central nervous system.

M. d'Avignon

***Svend G. Johnsen:* Adiposogenital dystrophy. A nosographic investigation based on a follow-up study of fat, feminine boys.**

Store Nordiske Videnskabsboghandel, Copenhagen, 1956, 376 pages.

In this comprehensive but easily read and captivating dissertation-work, conducted in the medical polyclinic at the Rigshospitalet in Copenhagen, the author presents a follow-up investigation of obese, effeminately built boys' development during adult age. The patient material comprises 184 cases of which there were 116 with the clinical diagnosis of dystrophia adiposo-genitalis. One group remained untreated and another group received relatively large doses of choriongonadotropin. The author maintains that the much disputed clinical entity dystrophia adiposo-genitalis actually exists, even in adult age. Cases presenting the characteristic clinical picture in boyhood showed in large numbers as adults an incomplete sexual maturity and in certain instances even a completely retained dystrophia adiposo-genitalis syndrome with total sexual infantilism. Other obese boys, who at the same age and by the same physicians were diagnosed as simple obesity, proved on the contrary as adults generally to possess normal virility and fertility. Further follow-up examinations made it abundantly clear that from earliest boyhood there already existed definite clinically demonstrable differences between these two groups, with the residual hypogonadism as the principal differential factor. Thus the diagnosis dystrophia adiposo-genitalis could be definitely made already in childhood. Besides hypogonadism and its sequelae, the author was able to reveal further signs of endocrine dysfunction in this syndrome. B.M.B. gave indefinite results and proved of no value for diagnosis. The presence of obesity seemed especially variable and no connection between hypogonadism and the degree of obesity could be established. In connection with puberty, obesity may often disappear completely or partly only to return later with an abrupt increment in weight when the subject is between 25 and 30 years of age.

The experiences gathered from the treated group turned out to be so decidedly positive that the author unconditionally, and for every case, recommends an intensive treatment with high doses (at least 40,000 units) of choriongonadotropin from an age as early as 10–12 years. The hormone therapy not only produced a symptomatic effect by accelerating puberty, but if intensely pursued it would also stimulate a permanently enhanced production of androgen and thus contrive to prevent a persistently grave genital hypotrophy with all its existential complications. Thus virility and genital maturity seemed to be favourably influenced while on the contrary no effect was exerted on the gravely reduced fertility. This form of therapy produced no unfavourable secondary effects.

The author considers obesity and hypogonadism as cerebrally conditioned, and obesity, because of nutritional needs, as a pathological hyperphagy. Various facts in

support of the cerebral origin are gleaned from a carefully selected literature and parallels are made with Frölich's syndrome. The author holds that the causation of the dystrophia adiposo-genitalis syndrome might be a hypothalamic dysfunction, of the same category as that encountered in Frölich's syndrome which presents similar gross anatomical changes.

B. Hagberg

H. Nowakowski: **Probleme der fetalen Endokrinologie. Drittes Symposium der deutschen Gesellschaft für Endokrinologie, Bonn, den 4. und 5. März 1955.**

Springer-Verlag, Berlin–Göttingen–Heidelberg, 1956, 225 pages.

A collocation comprising 22 lectures and sundry relevant discussions contributed to a symposium whose central theme was the reciprocal hormonal relationships in the maternal organism, the placenta and the foetus under normal and pathological conditions. Suggestive and competent general reviews are offered by A. Jost on "D'Analyse expérimentale de l'endocrinologie foetale", by A. Jores on "Wechselbeziehungen zwischen mütterlichem und fetalem Endokrinium", as well as by E. Philipp on "Die inkretorische Funktion der Placenta und ihre Wirkung auf den mütterlichen und fetalen Organismus".

The extraordinary central and dominant position of the placenta for the hormonal status of mother and foetus is strongly emphasized from various points of view. Not less than 8 out of 22 articles deal principally with the incretorial function of the placenta from different visual angles. From a paediatrical point of view the abovementioned general review by A. Jores is exceedingly interesting. It reviews systematically the effect on the foetus of sundry endocrine disturbances in the mother. Mention should also be made of W. Ehrengut's discussion of the true chromosomal sex of patients with the diagnosis of ovarial agenesis, of J. R. Bierich's discussion of "Entstehung und Symptomatik des kongenitalem adrenogenitalen Syndroms", as well as of the unusually suggestive discussions contributed in connexion with several lectures.

This book is handicapped like so many similar symposia collocations by a certain cumbrous orientation vis-à-vis the central core of the problem. A concluding summary of present-day knowledge of the principles of foetal endocrinology would have been of considerable value.

B. Hagberg

A. Perez-Soler: **La primo-infection tuberculeuse amygdalienne chez l'enfant.**

A. Karger, Basel. 1955, 60 pages, 28 figures. Sw. francs, 9. —/

Primary tonsillar infection is not a rare occurrence. During the past four years the author has studied 40 cases of evident or probable primary infection in the tonsils. Twenty-four cases were exhaustively studied and proved to be of aerogenous origin. In only 4 of these cases was the primary tonsillar lesion apparent. Tuberculosis in lymph glands appears to be the most constant clinical sign of primary infection in the tonsils which nearly always suppurate. The author maintains that all or nearly all of these cases were of human origin and aerogenously contracted. Bacteriological diagnostic examinations were not made to substantiate that supposition. In 4 children who succumbed with the infection and in 3 of whom post-mortem examinations were made, no other tuberculous lesions were found. The absence of primary tuberculous

lesions in the tonsils of these cases, and the origin of the tuberculous lymphatic glands in the neck through the lymphatics of the blood vessels, are discussed. Likewise comment is made on the calcification of the caseous glandular lesions. The author considers all large tuberculous glands in the neck near the maxillary angle to be primary, the port of entry being usually the tonsils, even if the latter fail to show primary lesions. The four fatal cases among the 24 infants were all very young. The author stresses that only the severest cases were sent to hospital. The mode of treatment accorded these patients is not stated in precise terms and it seems that it included surgical (tonsillectomy, adenoidectomy and extirpation of lymph glands), chemical, and radiological as well as general treatment.

***Advances i Pediatrics.* Vol. IX.**

Year Book Publishers, Inc., Chicago, Ill., U.S.A. 1957. $9.00.

The ninth volume of *Advances in Pediatrics* has maintained its customary high standard. Clifford in his paper on *postmaturity* stresses the point that only those cases complicated by placental dysfunction will be of real clinical importance as a cause of fetal and neonatal disease or death. The placental dysfunction syndrome consists in desquamating brown skin or unstained skin and in the appearance of having an "old and worried look". Careful observation of the postmature pregnant woman from an obstetric point of view is the most important prophylactic measure. Janeway and Gitlin have given us a brilliant survey of the present knowledge of the *gamma-globulins*. "Advances made by chemists during the few past decades in methods for separating and characterizing proteins . . . have fostered a revolution in biological and medical thinking." These words by the authors should have special interest for Tiselius' countrymen. The connection between antibodies, immunity and gamma-globulins is discussed and the occurrence of abnormal gamma-globulins is exemplified. The clinical syndromes of hypo- and hypergammaglobulinemia are reported in detail. *Thyroid disorders* in childhood are reported by Reilly. It is of interest that only 25 per cent of children with hypothyroidism before the age of 2 reach an IQ above 80. For those in whom the disease develops after this age the mental prognosis is better, i.e. 80 per cent reach an IQ above 90. The author recommends surgery as the method of choice in hyperthyroidism in childhood and puberty. *Familial dysautonomia* described by Riley has only been known as a clinical entity since 1949. The condition consists of a disturbance of the whole central nervous system. Crying without tears may be the symptom most often observed, but there are many other signs such as cold hands and feet, disturbed swallowing reflex. Familial occurrence has been reported in most of the cases. Schlesinger and Ast, both keenly interested in the fluoridation of water as a protection against *dental caries*, have given us a survey of the present conception of this problem. *Coagulation disorders* become more and more complicated as time goes on. Writing on this subject, two authors have here attempted to present an approach to "coagulation for the clinician". The Dutch team, Weijers, Kamer and Dicke, who in 1950 proved that wheat gluten gliadin is toxic for patients with *celiac disease*, has on this basis written an article on celiac disease in children. The determination of the fat retention is now possible by various new methods which are described in detail. The gliadin tolerance curve is another reliable diagnostic test. Pathogenesis as well as treatment and prognoses are discussed by the authors.

Edgar Mannheimer

Henry K. Silver, C. Henry Kempe and Henry B. Benga: **Handbook of Pediatrics.**

Lange Medical Publications. Los Altos, Calif. 1955 $3.00.

This handbook corresponds to what we Europeans call a pocket-book. It is of pocket-book size. The volume (450 pages) contains in abbreviated form the essentials of pediatrics. The first 10–12 introductory chapters give an excellent review of the principal general problems in pediatrics.

Horst Bickel and Fritz Souchon: **Die Papierchromatographie in der Kinderheilkunde.**

During recent years the great value of paper chromatography as an analytical method for the study of different metabolic disorders has been emphasized. Dr H. Bickel, one of the authors of this book, has made valuable contributions within this sphere. In this book he and Dr Souchon describe paper chromatographic analyses of amino acids and sugars especially with regard to childhood and metabolic disorders at that age.

K. Linneroth

Erik Freiesleben: **Erythroblastosis Foetalis. A Study of the History and the Antibody Titre. Thesis.**

Møllers Bogtrykkeri, Copenhagen, 1956. 177 pp.

The aim of the investigation was to show whether it is possible to establish certain principles for making a prognosis for Rh-positive children of Rh-immunized mothers. The material consisted of 315 Rh-positive children of Rh-immunized mothers, who were serologically examined at the State Serum Institute of Copenhagen from 1945 to 1954. The material was rather heterogeneous, the serological investigations were partly incomplete and the principles of treatment of the diseased infants varied. Accordingly, the material had to be divided into several smaller groups before the detailed analysis was made. The conclusions, however, are well-founded, and the investigation seems to explain satisfactorily some hitherto controversial phenomena.

The obstetric history and the child's condition were shown to be in distinct relation to each other. When there was no erythroblastosis in the mother's history there were many children without symptoms or with only mild symptoms, and only a few severe cases. When there was erythroblastosis in the history, but no still-births, the number of mild cases decreased and the moderate and severe ones increased. On the other hand, still-births in the history gave a high number of still-births. The probability of a still-birth when there was no erythroblastosis in the history was 17 ± 8 %. When there was erythroblastosis in the history, but no still-birth it was 20 ± 12 %, and with still-birth in the history, 62 ± 14 %.

A clear correlation was also revealed between the mother's terminal titre of antibodies and the condition of the child; the higher the titre the more serious was the disease. A few serious cases, however, did occur in spite of a low titre and no erythroblastosis in the history, and some mild cases occurred in spite of a high titre and a serious history.

The author was also able to demonstrate that in cases with the same titre, the child's condition was dependent on the history, and conversely, with equal histories, the condition was dependent on the titre.

The titre value at the beginning of the pregnancy was studied in relatively few cases. The author suggests that the initial titre is dependent on the history, and he assumes that the prognosis on the whole is dependent on the time the foetus is exposed to the antibodies and on the amount of antibodies passing through the placenta to the foetus.

By using the obstetric history and the maternal antibody titre it seems possible to get a rough estimate for the prognosis of the child of a Rh-immunized woman before pregnancy and at different stages of gestation.

For a pediatrician treating hemolytic disease of the newborn this thesis will be useful and is highly recommended.

Stig Sjölin

Lars Garby: **Studies on transfer of matter across membranes with special reference to the isolated human amniotic membrane and the exchange of amniotic fluid.** *Acta Physiol. Scand., 40,* **Suppl. 137, 1957.**

The purpose of the investigation has been to study, from a general physiological point of view, the permeability properties of the amniotic membrane and to examine the results in terms of amniotic fluid exchange in humans.

The work includes an examination of the theories of matter transfer across membranes in terms of "irreversible thermodynamics", a contribution to the theory of ordinary osmosis across leaky membranes, model experiments on matter transfer across artificial membranes and across the isolated human amniotic membrane. The diffusion resistance of the latter has been investigated using tagged species for water (D_2O), sodium (Na^{22}, Na^{24}), chloride (Cl^{36}), iodide (I^{131}), albumin (L^{131}-labelled), iron (Fe^{59}) and untagged creatinine and quinine. The electrical potential across the membrane and the resistance to liquid flow have also been measured.

With regard to the results obtained on the amniotic membrane, the following conclusions are drawn. This membrane exhibits a sieve-like function with respect to water-soluble species so that the majority of pores are of small dimensions, i.e. about 10–30 Ångström in diameter. The presence of a small number of larger pores, permitting the passage of protein molecules, has also been established. The number of pores of a size of 1000–10,000 Ångström in dimensions is negligible. The rate controlling structure of the membrane contains a surplus of negatively charged groups and facilitates the transfer of positive ions; also, it contains lipoid molecules that facilitates the transfer of lipoid-soluble molecules. The relative rates of passage of water and dissolved species are such as to permit an "osmotic" flow of liquid in the direction out of the amniotic cavity. The magnitude of this flow is estimated to be about 0.3–3 ml/hr. The net flows of NaCl, KCl and glucose in vivo are in the direction into the amniotic sac and approximately 0.3, 0.05 and 0.1 g/hr. The net flow of urea and creatinine are in the direction out of the amniotic sac and about 0.1 and 0.01 g/hr respectively. The large isotopic flows obtained by earlier investigators are interpreted as consisting mainly of self-diffusion.

Acta Pædiatrica 46: 534. Sept. 1957

ANNOUNCEMENTS

Children's Hospitals

Seminar held on June 7 to 9, 1956, at the International Children's Centre in Paris.

A full account of the reports and discussions on hospitals in large cities (cross infection, psychological problems, organization of the wards according to the children's age, general organization and working conditions), on the role of the hospital in organizing preventive medicine, on the training of hospital staff (teaching of pediatrics, training of child care nurses, welfare workers and administrative personnel), on problems connected with prolonged hospitalization of children (entertainment and education), on the hospitalization of children in special geographical conditions (small townships and regions with scattered population, tropical and sub-tropical regions).

The account, edited by Dr. J. Robineau, has been published in a special issue of the *Revue de l'Assistance Publique à Paris*, 8th year, No. 45, January–February 1957, on sale at the International Children's Centre. Price 500 francs for France, and 600 francs for other countries.

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